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Experimental Brain Tumors

I. Tumors Produced with Methylcholanthrene*

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Efforts to produce intracranial neoplasia by various chemical carcinogens have been attended with scant success prior to the work of Seligman and Shear (2). By intracerebral implantation of pellets of 20-methylcholanthrene, these workers produced 11 gliomas and 2 fibrosarcomas in a series of 20 male mice of the C3H strain. Seligman and Shear reported also successful subcutaneous transplantation of several of these tumors, one of which was stated to be a glioma.

Utilizing the same technic, the present writers reported a preliminary experiment (3) in which they found 26 intracranial tumors in 51 C3H mice. These tumors, occurring during the first 10 months of the experiment, consisted of oligodendroglioma, glioblastoma multiforme, medulloblastoma, unclassified glioma, and meningeal sarcoma.

More recently Peers (1) implanted cholesterol pellets containing 10 per cent methylcholanthrene in the brains of 99 mice, of which 87 survived into the tumor-bearing period. In all, 32 intracranial tumors were produced—17 sarcomas and 15 gliomas.

These observations were significant in that they suggested the future possibility of studying the incidence, histiogenesis, and growth behavior of experimentally induced primary brain tumors. From such a study it was felt that certain deductions could be drawn regarding the human counterparts of these neoplasms. The present investigation was thus undertaken for a threefold purpose; namely, the determination of the incidence, the histiogenetic origin, and the growth behavior of experimental brain tumors.

MATERIALS AND METHOD

Care of animals.—All the animals employed in these experiments were male mice of the C3H strain between 3 and 4 months of age. They were housed in groups of 4 in pyrex glass jars having wire mesh covers. The jars were sterilized weekly. Each group of animals was inspected at least twice daily for evidences of tumor development.

The diet consisted of Purina Fox Chow and oats. This and tap water were available to the animals at all times ad libitum.

Carcinogen.—The carcinogen employed for intracranial implantation was 20-methylcholanthrene (Hoffman-LaRoche, Inc., Nutley, N. J.) which was purified by chromatographic adsorption on Al_2O_3.[1] The specimen used had a corrected melting point of 179.8-180.4° C. Cylindrical pellets of this hydrocarbon were prepared with a diameter of about 1 mm. and a length of about 1.5 mm., the average weight of each pellet being 1.5 mgm.

Operation.—Anesthesia was accomplished by the subcutaneous injection of 0.25 cc. of a solution containing 100 mgm. nembutal in 15 cc. of 0.9 per cent sodium chloride solution. The top of the head was shaved and washed with 70 per cent alcohol. For intracerebral and subdural implantations a right paramedian incision 5 mm. in length was made in the skin; the periosteum was scraped off the right parietal bone; a hole about 2 mm. in diameter and anterior to the occipital suture was made in this bone with a dental burr. For intracerebellar implantations the scalp incision was made in the midline over the occipital bone and the burr hole in the area between the occipital suture and the attachments of the occipitalis muscles. Muscle bleeding, which sometimes occurred in this location as the result of trauma, was readily controlled with hot wet sponges. With fine forceps the pellets were pushed through the craniotomy opening and dura for about 3 mm. into the right parietal lobe subcortex or into the cerebellum. Those intended for subdural implantation

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[1] The purified methylcholanthrene was kindly prepared for us in the laboratory of Dr. M. J. Shear of the United States Public Health Service.

were left in the longitudinal fissure in contact with the meninges between the two cerebral hemispheres. The skin margins were then approximated and a drop of collodion was applied over the wound. This never required any further attention, healing occurring promptly and without infection. Until full recovery from the anesthetic, which usually occurred in from 2 to 3 hours, the animals were kept warm on a padded hot plate which was set at about 40° C. When recovery was complete, the mice were returned to their cages in the specially ventilated and heated animal room.

Subcutaneous transplantation of tumors.—To study certain phases of the growth behavior of the cerebral neoplasms more effectively, subcutaneous transplantation of a number of these tumors was made into male and female mice of the C3H strain. The animals used were 2 to 3 months of age and the sexes were represented in about equal numbers. Mating was prevented by strict segregation. As a rule, 8 mice received transplants from each tumor, although in some instances 4 mice were used. Subtransplants were made from the subcutaneous growths when the latter attained sizes of 1 cm. or more in diameter, subtransplantation being carried out through 9 to 14 passages. These mice received the same general care and food as those in which the pellets of methylcholanthrene were implanted.

The material used for subcutaneous transplantation consisted of a piece of tissue removed from the main tumor mass, with careful avoidance of obviously necrotic and hemorrhagic areas. This was cut in sterile saline into fragments about 1 mm. in diameter. The fragment of tumor tissue was deposited in the subcutis of the right axillary region or in the right flank by means of a trocar introduced into the right groin through skin washed with alcohol.

Necropsy technic.—Mice which were moribund were invariably killed by sectioning the cervical spinal cord and a complete necropsy was performed immediately thereafter. The brain was removed with sterile precautions and, when a tumor was encountered, a piece was usually excised for subcutaneous transplantation. The brain was then fixed in neutral formalin (U.S.P. formaldehyde 1:10). Animals which were found dead were necropsied immediately on discovery and the brains fixed in the same manner. It proved expedient in a few instances, because of onsetting post-mortem softening, to harden the contents of the partially opened crania in the fixative for 24 hours before removing the brains. Since tumors were not found in any of the other viscera of these animals the organs were not saved.

With a few exceptions the brains were embedded in paraffin and sectioned serially. Hematoxylin-eosin was the stain employed routinely, but at regularly spaced intervals sections were prepared with the Masson trichrome stain and with the Wilder silver carbonate method for reticulin. Where it seemed indicated, preparations were stained with Heidenhain's iron-hematoxylin and with phosphotungstic acid-hematoxylin. Frozen sections impregnated with silver and gold salts offered such little additional aid in histologic study that their preparation was abandoned early.

Results

For purposes of convenience in presentation, the data of this study will be presented in two parts; I. the results of the intracranial implantation of the methylcholanthrene pellets and, II. the subcutaneous transplantation of the intracranial neoplasms thus induced.

I. Intracranial Implantation of Methylcholanthrene

The pellets of methylcholanthrene were implanted in three different locations in groups of mice as follows: the right parietal subcortex, 57 mice; the cerebellum, 30 mice; and the subdural space, 16 mice. The incidence of the various types of neoplasms as they occurred at the different sites of pellet implantation in the three groups of the 103 mice of this experiment is shown in Table I.

Table I: Incidence of Brain Tumors Induced with Methylcholanthrene According to Site of Pellet Implantation

	Group I (Cerebrum)	Group II (Cerebellum)	Group III (Meninges)
Total number of animals	57	30	16
Negative for tumor	31	17	7
Total number of tumors	26	13	9
Unclassified tumor	1	2	..
Gliomas	15	8	2
Astrocytoma	1	..	..
Glioblastoma multiforme	4	2	..
Medulloblastoma	1	3	..
Oligodendroglioma	3	..	..
Spongioblastoma polare	..	..	1
Unclassified glioma	5	3	1
Multiple gliomas	1	..	..
Sarcomas	5	1	7
Rhabdomyosarcoma	2	..	6
Meningeal sarcoma	2	..	1
Cerebral sarcoma	1	..	..
Mixed sarcoma and glioma	5	2	..

Extreme conservativism was employed in the classification of the neoplasms, which accounts for the fact that such noncommittal designations as *unclassified tumor* and *unclassified glioma* appear in Table I. The three tumors under the first designation, although genuine neoplasms as indicated by their invasiveness and the presence of cells in mitosis, were nevertheless too small to permit more detailed study and classification. The ten tumors designated as *unclassified glioma* were

large enough to permit special study. None of them contained reticulin fibers and, although glial elements were identified in all, they failed to present such characteristic architectural patterns as are requisite for the classification of tumors of the glioma group. As an unclassified glioma, for example, is listed the tumor of mouse No. 74, which will be described in some detail later and which had certain features of glioblastoma multiforme. To avoid arbitrariness, however, this tumor was left unclassified.

In one instance, mouse No. 11, the brain tumor was found to consist of two distinctly different component parts—one, oligodendroglioma and the other, glioblastoma multiforme. This is not to mean that oligodendroglia cells were found scattered in a tumor that otherwise resembled a glioblastoma, but rather that two different tumors were found side by side. In Table I, these new growths are listed as *multiple gliomas*. In the same sense multiple tumors composed of gliogenous and sarcomatous portions were also discovered. These, 7 in number, are classified as *mixed sarcoma and glioma* in Table I.

Space does not permit a detailed description of each of the neoplasms produced, but representative tumors will be described below.

Glioblastoma multiforme.—Mouse No. 14. This animal died 207 days after the intracranial implantation of the hydrocarbon. At necropsy the methylcholanthrene pellet (MCA) was found buried deep in the right parietal lobe, which was replaced in large part by a hemorrhagic neoplasm measuring 1 cm. in diameter (Figs. 1-A and 1-B). This tumor eroded the overlying calvarium and lay as a flattened, partially necrotic, and partially calcified mass beneath the scalp. It was composed of pleomorphic cells, many of which had bipolar processes. These cells were frequently arranged in pseudopalisades around foci of necrosis (Fig. 1-C). Many were in mitotic division and many were multinucleated, some nuclei containing spheroid, pink-staining structures resembling inclusion bodies (Fig. 1-D). The choroid plexus of the right lateral ventricle was infiltrated with tumor cells and the leptomeninges likewise contained clusters of these cells. There was no stroma of reticulin in this neoplasm as demonstrated by the Wilder silver impregnation method (Fig. 1-E).

Mouse No. 40. This animal survived 314 days the pellet implantation in the cerebellum. At necropsy the calvarium was found intact, but much of the cerebellum was replaced by a gray, semigelatinous, infiltrating glioma (Figs. 2-A and 2-B). Many of the cellular elements of this tumor were identified as unipolar and bipolar spongioblasts, but other glial elements such as astrocytes were also present. There were moderate numbers of cells in mitotic division and of multinucleated giant cells. Numerous zones of necrosis were seen around which spongioblasts were arranged in pseudopalisades (Fig. 2-C). Small foci of hemorrhage and of calcium salt deposition were found scattered in the tumor. The neoplastic cells had infiltrated the leptomeninges and extended along the Virchow-Robin spaces into the nervous parenchyma (Fig. 2-D). There was no evidence of a vascular proliferative reaction. What little stroma was visible in the neoplasm was not formed by reticulin, as the Wilder preparations revealed (Fig. 2-E).

Medulloblastoma.—Mouse No. 52. This mouse died 295 days after the intracerebellar implantation of methylcholanthrene and after a course which was characterized by disturbances of balance and paralysis of the left hind leg. At necropsy, the brain was found adherent to the skull. The cerebral hemispheres were uninvolved, but the left half of the cerebellum was bulging and brown in color. On section it was seen that this was due to a hemorrhagic and semigelatinous tumor mass surrounding the pellet (MCA) (Figs. 3-A and 3-B).

The microscopic picture revealed an infiltrating glioma composed of a remarkably uniform type of cell. This had a prominent oval or round nucleus of medium size with numerous chromatin granules. The cell body had scant cytoplasm and was inconspicuous. There were no cellular processes. Cells of this variety were frequently arranged in pseudorosettes (Fig. 3-D). Mitotic division was present in abundance. The tumor had almost no stroma; the Wilder preparations were negative (Fig. 3-C). Calcium salt deposits were found in several regions (Fig. 3-E). There was widespread invasion of the cerebral leptomeninges and of the Virchow-Robin spaces in many parts of the brain. Tumor cells were found in the fourth ventricle, the aqueduct of Sylvius, and the third ventricle (Fig. 3-F).

Mouse No. 49. This mouse was killed 296 days after methylcholanthrene was implanted in the cerebellum, when the animal developed paralysis of both hind legs and a disturbance in balance which was characterized by a tendency to fall to the left in walking. The cranial sutures were found separated at necropsy, which accounted for a slight increase in the size of the head of this animal. The hydrocarbon was found embedded in a somewhat gelatinous tumor mass replacing the left half of the cerebellum (Fig. 4-A). Part of this tumor was removed for transplantation in other mice, the results of which will be reported below.

The tumor was found microscopically to be poorly demarcated from the surrounding cerebellar parenchyma and was composed of a remarkably uniform type of cell. The latter resembled in all important features the cell described in mouse No. 52 (Figs. 4-B and 4-C). For the most part the neoplastic elements failed to form any definite architectural pattern, lying helter-skelter, but a faint suggestion of pseudorosette formation was seen in some regions. The nearby meninges and choroid plexus were infiltrated with tumor cells (Fig. 4-D). The stroma was scant and indifferently stained; Wilder preparations were negative (Fig. 4-E).

Oligodendroglioma.—Mouse No. 16. The animal died 366 days after pellet implantation in the right cerebral hemisphere where, at necropsy, a gray, opaque, and partly hemorrhagic tumor was found (Figs. 5-A and 5-B). The midline of the brain had shifted to the left. An infiltrating glioma was found, microscopically composed of cells having an exceptionally uniform appearance. They were of small size with scant, pink-staining cytoplasm and small, dark, round nuclei (Fig. 5-C). Frequently the nuclei seemed to lie naked in clear, unstained halos, but occasionally they were surrounded by narrow rings of cytoplasm which lay within the halos. Some of the cells were in mitotic division. The tumor was hemorrhagic in spots but was devoid of reticulin.

Spongioblastoma polare.—Mouse No. 55. Four days before this animal was found dead on the 314th day of the experiment, its head was noted to be peculiarly deformed. Necropsy disclosed this to be due to a bulge of the cranium in the right parietal region due to a large tumor mass which replaced most of the right cerebral hemisphere (Fig. 6-A). The pellet of methylcholanthrene presumably had been placed in the subdural space in contact with the meninges, but it could not be located there at necropsy, nor could it be found in the cerebral tumor mass.

The histologic picture of the intracerebral neoplasm (Fig. 6-B) revealed invasiveness and a number of deep-seated hemorrhages.

Large zones were composed of parallel rows, bands, or whorls of spindle-shaped cells with elongated nuclei and bipolar processes. These cells resembled spongioblasts. Intermingled with them were medium-sized cells with uniform dark nuclei (Fig. 6-C). A few calcium salt deposits were encountered in this portion of the tumor. In other parts there were present closely packed bizarre-shaped giant cells, some multinucleated (Fig. 6-D). The cytoplasm of these cells was abundant and formed prominent processes. There were many glia cells in mitotic division. The tumor had very little stroma, none of it of mesodermal origin as the negative Wilder stain proved (Fig. 6-E).

Multiple gliomas.—Mouse No. 11. The animal was found dead on the 192nd day of the experiment. On reflecting the scalp, a tumor mass of about 4 mm. diameter was found protruding through the skull at the site of the trephine wound. It was found originating in the right cerebral hemisphere, destroying the basal ganglia and shifting the midline to the left (Figs. 7-A and 7-B). There was some hemorrhage in this tumor and some necrosis.

Microscopically the neoplasm was composed of several different zones. In one, the cells were nearly all spongioblasts, the processes of which pointed to centers of necrosis. These cells were arranged in pseudopalisades (Figs. 7-C and 7-D). The endothelial cells of many blood vessels were proliferated. Giant cells and mitotic figures were present in small numbers. The cell constituents and architecture were typical of *glioblastoma multiforme*. In other large areas the tumor cells contained round, remarkably uniform nuclei surrounded by clear halos (Fig. 7-E). Here mitotic figures were rare. These portions of tumor represented *oligodendroglioma*.

Meningeal sarcoma.—Mouse No. 83. A tumor appeared beneath the scalp on the 312th day of the experiment. During the next 3 days it increased so rapidly in size that it was deemed essential to kill the mouse in order to save material for subcutaneous transplantation. The vertex of the skull was eroded by a neoplasm which arose in the longitudinal fissure region near the pellet in the right parietal lobe (Fig. 8-A). The carcinogen was embedded in the base of the tumor which had a loose structure and seemed to arise from the leptomeninges. Its cells were bipolar and had long processes. The nuclei were oval or elongated and contained many large chromatin granules. There were many mitotic figures. The neoplastic cells were arranged in long strands or in whorls, frequently around capillaries (Fig. 8-B). A delicate reticulin network permeated the whole neoplasm including the whorls (Fig. 8-C), but there were no collagenous fibers.

Cerebral sarcoma.—Mouse No. 10. Two days before this animal was killed on the 372nd day of the experiment, a small tumor appeared on the top of the head beneath the scalp. At necropsy this tumor nodule was found to be an extension through the craniotomy wound of a much larger tumor mass in the right parietal lobe (Figs. 9-A and 9-B). The neoplasm was gray in color, firm in texture, and lay above the pellet of methylcholanthrene which was partially submerged in the right lateral ventricle. The midline of the brain was shifted to the left; the right cerebral hemisphere was compressed by the neoplasm, a portion of which was utilized for subcutaneous transplantation.

The cells forming this tumor were of two types (Fig. 9-C). One had large, pale vesicular nuclei, one or two nucleoli, and a moderate amount of pale cytoplasm. The other had small, dark, round nuclei and inconspicuous cytoplasmic bodies. There was no characteristic architecture. The stroma was scant, but was readily impregnated with silver in the Wilder preparations (Fig. 9-D). There were no collagen fibers.

Mixed sarcoma and glioma.—Mouse No. 44. On the 222nd day of the experiment this animal succumbed to a cerebellar neoplasm which arose at the site of the pellet implantation (Figs. 10-A and 10-B). It was apparent that the bulk of the tumor within the cerebellum itself was composed of small round cells forming one distinctive pattern and that the outer, cap-like portion of the tumor was composed of densely packed spindle-shaped cells forming another pattern (Figs. 10-B and 10-C).

In the larger portion the cells were easily identified as oligodendroglia (Fig. 10-D). They were round and small with intensely stained, round nuclei surrounded by halos of pale or unstained cytoplasm. Occasional astrocytes were present as well as groups of multinucleated cells and cells in atypical mitotic division. This part of the neoplasm contained no reticulin fibers (Fig. 10-E).

The smaller, dorsally lying portion of tumor was definitely of mesodermal origin. Its cells had oval, chromatin-rich nuclei and bipolar processes (Fig. 10-F). The stroma of this portion was readily impregnated with silver by the Wilder method for reticulin (Fig. 10-G).

II. SUBCUTANEOUS TRANSPLANTATION OF EXPERIMENTALLY PRODUCED BRAIN TUMORS

The following section includes descriptions of representative cases of successful transplantation of various induced brain tumors.

Medulloblastoma.—Mouse No. 49. The tumor of this animal was described above as an example of an invasive malignant cerebellar neoplasm which was classified as a medulloblastoma. Reference to the description of this tumor and to Fig. 4 in which it is illustrated will, perhaps, raise some doubt as to the justification for this classification. The results of subcutaneous transplantation, however, leave no doubt on this point and demonstrate the value of this method of study, especially in difficult cases.

In Fig. 11-A is shown the tumor which developed in 45 days after implantation in the subcutaneous tissues of the right flank. Subtransplantation was carried out in 10 generations, involving a total of 44 animals. In general, the microscopic appearance of the transplants resembled rather closely the primary neoplasm, but the characteristic architecture was more pronounced. Thus, pseudorosette formations were more numerous and better formed (Fig. 11-B). It is of interest to note that in spite of the fact that the gliogenous tumor grew in the subcutaneous tissues, it grew as a "pure" medulloblastoma uncontaminated by mesodermal elements (Fig. 11-C).

Unclassified glioma.—Mouse No. 74. Reference has already been made above to the problem presented by this tumor. The primary neoplasm appeared in the right parietal lobe 240 days after the implantation of the carcinogen. The microscopic structure of the tumor (Fig. 12-A) was densely cellular with poor demarcation from the surrounding brain tissue. There was great cellular pleomorphism with many cells identifiable as astrocytes, spongioblasts, and even medulloblasts. Cells in mitotic division were seen frequently; however, no characteristic architecture was present to aid classification. Tumor cells were found diffusely infiltrating the leptomeninges (Fig. 12-B).

The first subcutaneous transplant revealed tumor cells of two varieties. One was a rather small cell with scant cytoplasm and round, chromatin-rich nucleus. Groups of such cells had a tendency to form pseudorosettes (Fig. 12-C). The other was a larger cell with a vesicular nucleus and a conspicuous cytoplasmic body from which originated many processes. In hematoxylin-eosin preparations the latter cell type resembled epithelioid cells which were frequently arranged in wide bands around blood vessels in the manner of astroblasts. This is illustrated in Fig. 12-D, which is derived from the 11th subcutaneous sub-

transplant. Multinucleated giant cells, like those seen so frequently in glioblastoma multiforme, were present in small numbers in all of the 12 generations of transplants from this tumor (Fig. 12-E).

A total of 96 mice received subcutaneous transplants from this neoplasm, only 5 mice in all revealing a completely similar tumor architecture. The fluctuation in the histologic appearance from one generation of transplants to another made a rigid diagnosis of the tumor unwarranted, but certainly the resemblance to glioblastoma multiforme was the most frequently observed.

Astrocytoma.—Mouse No. 69. After 270 days this animal succumbed to the neoplasm which arose in the right parietal lobe at the site of methylcholanthrene implantation (Fig. 13-A). The eyes were constantly closed during the last days of life and the head was misshaped from the tumor growth and as a result of the separation of the cranial sutures.

At necropsy the tumor was found involving both hemispheres, and the pellet was located in the subcortex at the junction of frontal and parietal lobes. This tumor had a gelatinous consistency and was poorly demarcated from the surrounding brain tissue. It consisted of cells whose cytoplasm was scant and gave rise to multipolar processes. The nuclei were intensely stained and often had one or more nucleoli. Frequently they were arranged around spaces containing homogeneously pink-staining (in hematoxylin and eosin preparations), colloid-like material (Fig. 13-B). Cells in division were rather numerous and occasional large bizarre elements were also seen. There was no invasion of the meninges except for one small focus. The vast majority of the cells were thus readily identifiable as astrocytes, although the cellular division was a discordant feature. Mesodermal constituents were absent (Fig. 13-C).

A series of 10 subtransplants involving 48 mice was made of this neoplasm. In general, the microscopic features of the transplants were similar to those in the original tumor. There were seen the same cystic spaces filled with coagulated material and the same multipolar astrocytes. In addition, however, the cells began to assume a pseudorosette formation in the second subtransplant (Figs. 13-D and 13-E) which became progressively more distinct in subsequent subtransplants and reached its full development in the 7th generation (Fig. 13-F). Here the pseudoglandular structure was quite conspicuous and was strongly suggestive of the human "piloid" or "malignant" astrocytoma.

Meningeal sarcoma.—Mouse No. 83. The primary tumor which this animal developed at the site of the implanted carcinogen received attention above. Its histologic appearance was that of a reticulin-forming sarcoma whose cells had a tendency to form whorls. Transplantation of this tumor was carried out through 8 generations, involving a total of 44 mice. The invariable microscopic picture seen in the transplants was that of strands of elongated spindle-shaped cells sometimes caught in a longitudinal and sometimes in a transverse plane (Fig. 8-D). At no time were the whorls of the original tumor encountered. Numerous cells were in division and connective tissue reticulin was produced abundantly (Fig. 8-E).

Cerebral sarcoma.—Mouse No. 10. The primary tumor which this mouse developed was described above. It consisted of two cell types, a large and a small, in a scant argentophile stroma. There was no characteristic architectural pattern. A total of 32 mice received transplants from this neoplasm, its perpetuation being voluntarily stopped at the end of the 6th generation. Practically all the transplanted tumors showed a predominance of the large cells, many of which were in mitotic division (Fig. 9-F). A characteristic structure failed to develop although reticulin continued to be formed in small amounts (Fig. 9-E).

Mixed sarcoma and glioma.—Perhaps the greatest value of the technic of subcutaneous transplantation was demonstrated for the group of mixed tumors, an example of which is mouse No. 106. At 177 days of the experiment the head of this animal was malformed by a bulging tumor mass which had its origin in the right parietal lobe and had eroded the overlying calvarium to present itself beneath the scalp (Figs. 14-A and 14-B). The tumor was firm, fleshy, and gray. It had produced a shift of the midline of the brain to the left.

The microscopic appearance of the neoplasm was difficult to evaluate since it presented a confused mixture of several different types of cells. Many small round elements were present which had deeply stained nuclei and scant cytoplasmic bodies (Fig. 14-C). Large numbers of these cells were in different stages of mitotic division. Here and there were noted giant cells with more than one nucleus. In the background of these cells were found interlacing strands and whorls of spindle-shaped elements with elongated nuclei and cytoplasmic bodies that seemed to give origin to a fibrillary stroma. Some of these cells were also in mitotic division. The absence of a characteristic structural pattern microscopically precluded a diagnosis of this tumor.

Portions of the primary neoplasm were transplanted subcutaneously into 8 mice, 7 of which developed local tumor growths only after more than 4 weeks. In all 7 mice the transplanted tumors differed considerably from the primary tumor. In 5 of the mice the microscopic appearance of the neoplasm was that of spindle-shaped cells forming strands and whorls (Fig. 14-D) in an abundant stroma of reticulin fibers (Fig. 14-E). The tumors of the remaining 2 mice, although similar to each other, differed entirely from those just described. They consisted of uniformly round, small cells with deeply stained nuclei and a minimum amount of stroma (Fig. 14-F). Many of these cells were dividing and there was a definite tendency for them to be arranged around blood vessels or tissue spaces in the form of pseudorosettes. Reticulin could not be demonstrated in either of these tumors (Fig. 14-G).

Thus it was shown conclusively that the primary neoplasm was composed in part of mesodermal and in part of gliogenous elements. Unfortunately, subtransplants were made only of the mesodermal tumor, which went through 9 generations in a total of 37 mice. In each animal the tumor remained a "pure" sarcoma without a gliogenous component. From the previous experiences with subcutaneous transplants of gliomas there is no reason to suspect that the gliomatous portion of the primary neoplasm could not have been perpetuated had subtransplants been made.

Discussion

The incidence of brain tumors induced by the intracranial implantation of methylcholanthrene in C3H male mice was 46.6 per cent (48 out of 103 mice). The pellets of carcinogen were found within the cranial cavities in association with the neoplasms in the animals which developed tumors and were embedded in normal tissue in the mice which failed to develop them. Yet the pellets removed from both the positive and negative tumor groups were equally effective in inducing brain tumors later when implanted in other C3H mice. This experience suggests that other factors in addition to the carcinogen are important in the induction of tumors. Also the fact that only 46 per cent of the mice developed brain tumors points to factors, in addition to the carcinogen, which influence tumor production. The present experiment, however, was not devised to throw light on this question.

It was originally felt that the site of origin of the brain tumor might influence its type and it was for this

reason that the pellets of carcinogen were implanted in 3 different locations; namely, in contact with the meninges, the cerebrum, and the cerebellum. Of the 9 tumors which developed in the first named location, 7 were sarcomas, as was to be expected, and 2 were gliomas. In each of the latter 2 instances, however, the pellet actually came in contact with the nervous parenchyma. The converse of this also occurred; namely, the development of sarcomas following the implantation of pellets in the cerebrum. Thus, even 2 rhabdomyosarcomas were produced, but this undoubtedly could be ascribed to the fact that the carcinogen had worked its way out through the burr hole and came to lie in contact with the temporalis muscle.

Of the gliomas that were produced in the cerebrum, only 2 examples need special mention. One was the medulloblastoma, an unusual site for this tumor, and the other was the instance of multiple gliomas. In the cerebellum, the glioblastomas that were found there could not have been anticipated, but the 3 medulloblastomas were entirely in keeping with clinical experience. With certain definite reservations, therefore, it could be stated that the site of origin of the neoplasm had an influence in determining its type. This, however, is not to be interpreted as implying that any considerable light has been shed on the histiogenesis of the gliomas. That still remains a moot question. It was at first hoped that a study of the beginnings of a glioma in a young tumor would explain its histiogenesis. In reality, however, the malignant cells in early stages were unidentifiable with respect to the subsequent type of tumor and remained so until they proliferated sufficiently to produce a recognizable architectural pattern. The subcutaneous transplants aided almost as much in the study of the histiogenesis as of the growth behavior of these tumors, but it is still not possible to state what the factors are which determine whether a given glial cell will form an astrocytoma, an oligodendroglioma, or any other type of glioma.

A striking difference was noted in the rate of development between the primary sarcomas and gliomas. Of the 13 sarcomas, the first appeared on the 125th day and the last on the 372nd day. The average, however, was 195 days and, more striking still, was the mean of 165 days. Of the 25 gliomas, the first was noted on the 127th day and the last on the 378th day. The average day of appearance was the 279th and the mean, the 330th day. Accurate determinations of the first appearance and the rates of growth of the tumor transplants were not made, but the generalization is justified that the gliomas grew much more slowly than the sarcomas. Signs of growth of the latter tumors were often noted within 3 weeks, whereas the gliomas frequently took at least twice this time.

It is of some interest to note with what great facility the glioma transplants grew in their new mesodermal environment. This is perhaps all the more surprising since it is a well known fact that the human tumors of this variety are never found as extracranial metastases. Apparently there is no local tissue resistance against the ectodermal gliomas, but rather an absence of an available pathway for metastasis. Even the most malignant of the gliomas fail to invade blood vessels.

Among the more interesting results of these experiments were those obtained with the transplantation of the tumors designated as mixed sarcoma and glioma. In transplants it proved possible to grow the constituent parts of these neoplasms in pure form; *i.e.*, as glioma or sarcoma. The subtransplants of these "purified" tumors remained true in many subsequent generations. Such results are comparable to the every day experience of the bacteriologist who subcultures colonies from a mixed bacterial growth to obtain several pure strains of organisms.

Summary and Conclusions

Pellets of purified 20-methylcholanthrene were implanted in the cerebral meninges, the right cerebral hemisphere, and the cerebellum of 103 C3H mice of the male sex.

In all, 48 tumors were produced in this manner: 25 gliomas, 13 sarcomas, 7 mixed gliomas and sarcomas, and 3 unclassified. Among the gliomas were present examples of astrocytoma, glioblastoma multiforme, medulloblastoma, oligodendroglioma, and spongioblastoma polare. Within certain limits the site of pellet implantation was a determinant of the type of intracranial neoplasm which developed.

The rate of growth of the sarcomas was much greater than of the gliomas. The average time when the sarcomas appeared was 195 days as against 279 for the gliomas.

The method of subcutaneous transplantation was employed for the study of the growth behavior of these intracranial neoplasms. From 9 to 14 subtransplants were made of many of these tumors with results that indicated a much more rapid growth of the sarcomas than the gliomas. Frequently, unclassifiable primary gliomas developed characteristic structural patterns in the transplants which made identification possible. This method of study also permitted the separation of so-called "mixed" tumors into their component parts.

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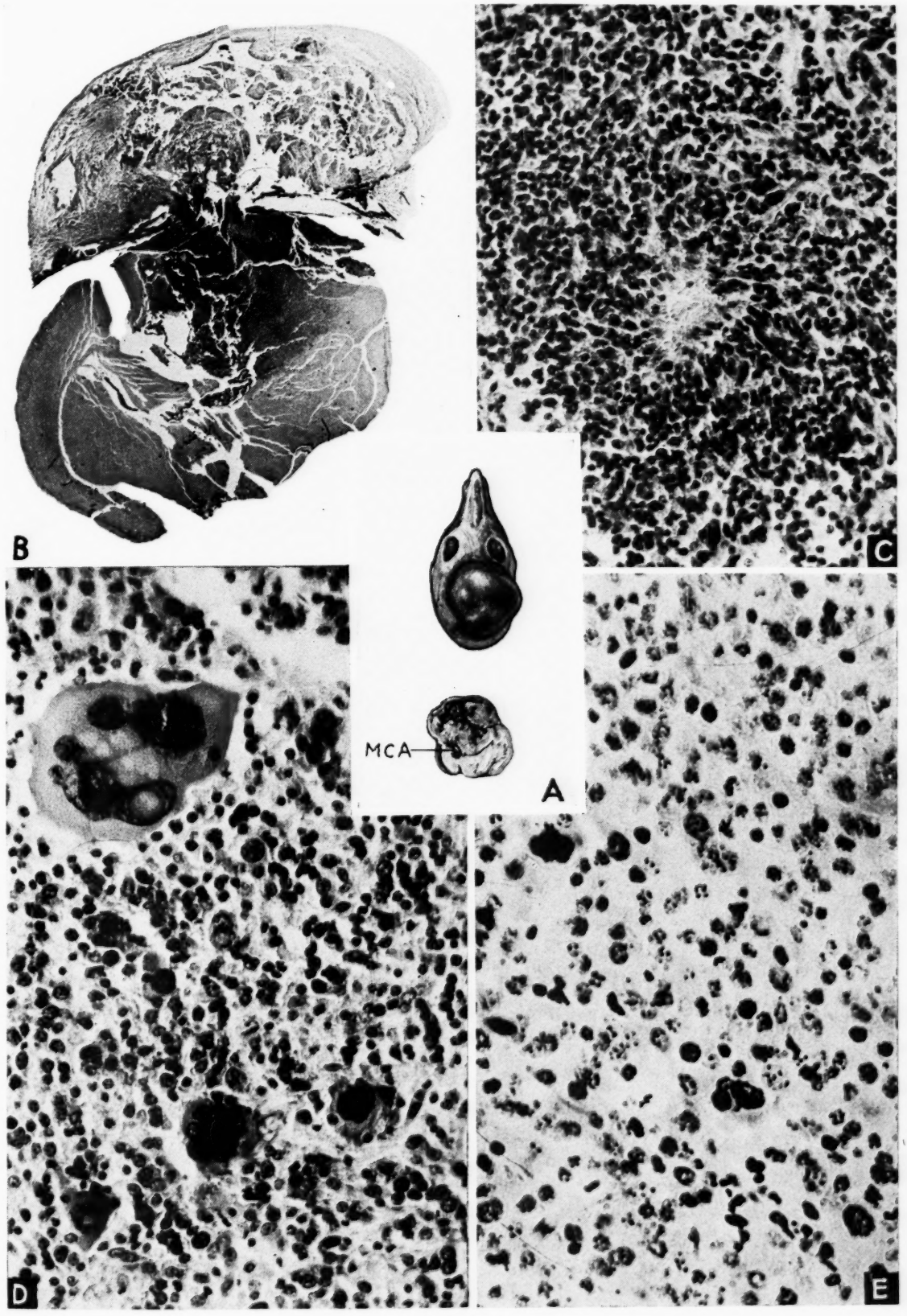

FIG. 1.—Mouse No. 14. Glioblastoma multiforme. A. Pellet of methylcholanthrene (MCA) deep in right parietal lobe and surrounded by tumor. Note extracranial position of neoplasm in upper figure. B. Transverse section of brain showing intracerebral and extracranial portions of tumor. H & E stain *; mag. × 6. C. Pseudopalisade around focus of necrosis. H & E stain; mag. × 200. D. Multinucleated giant cells. Note pale spheroid structure resembling inclusion body in nucleus of upper giant cell. H & E stain; mag. × 270. E. Absence of reticulin fibers. Wilder stain; mag. × 400.

* Hematoxylin and eosin stain abbreviated in legends as H & E.

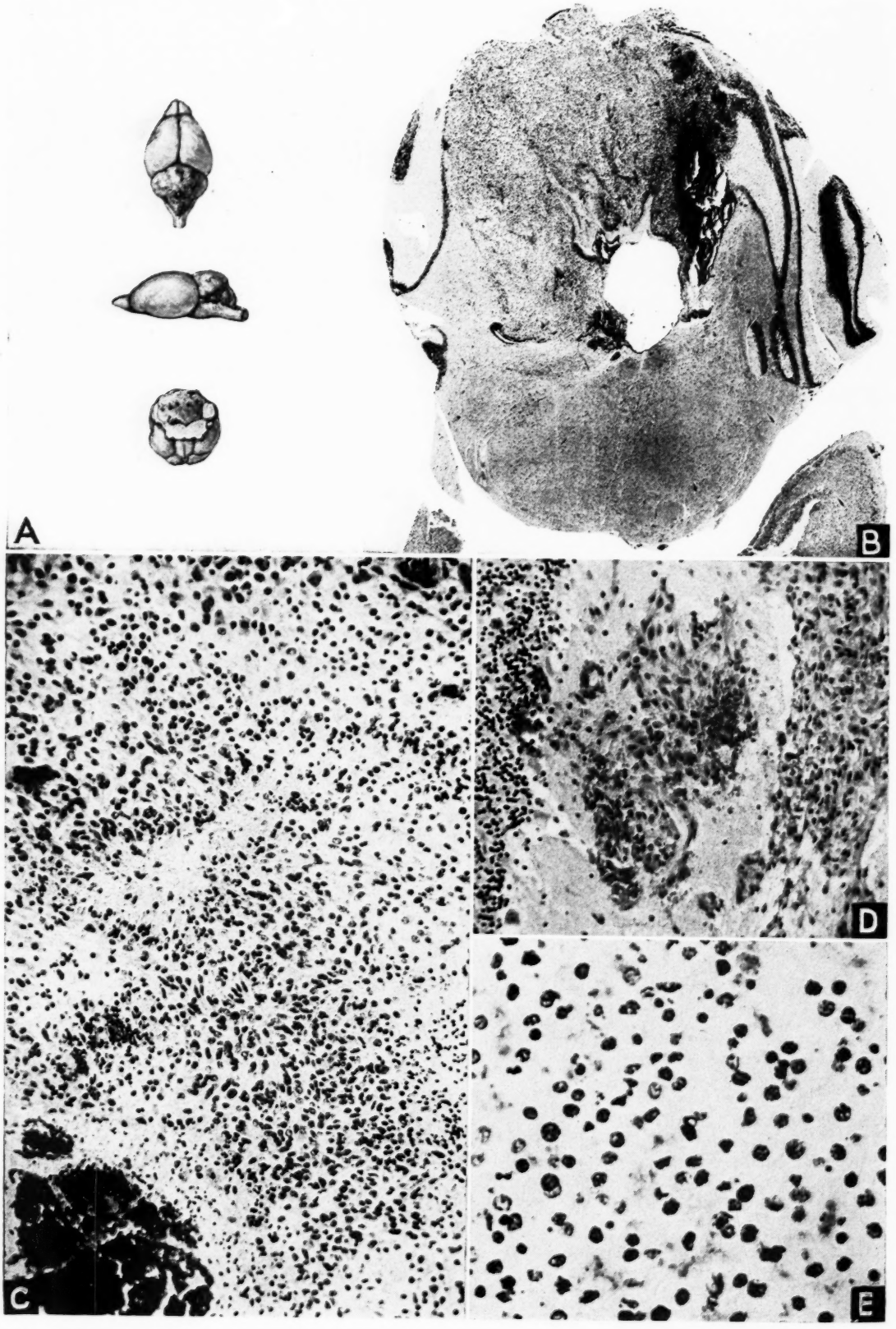

FIG. 2.—Mouse No. 40. Glioblastoma multiforme. A. Drawing of tumor in cerebellum. B. Photomicrograph of cerebellar neoplasm. Clear space represents site of methylcholanthrene pellet. H & E stain; mag. × 8. C. Pseudopalisading of cells. Calcification in lower left corner. H & E stain; mag. × 160. D. Tumor cells invading leptomeninges and molecular layer of cerebellar cortex. H & E stain; mag. × 160. E. Absence of reticulin in tumor. Wilder stain; mag. × 500.

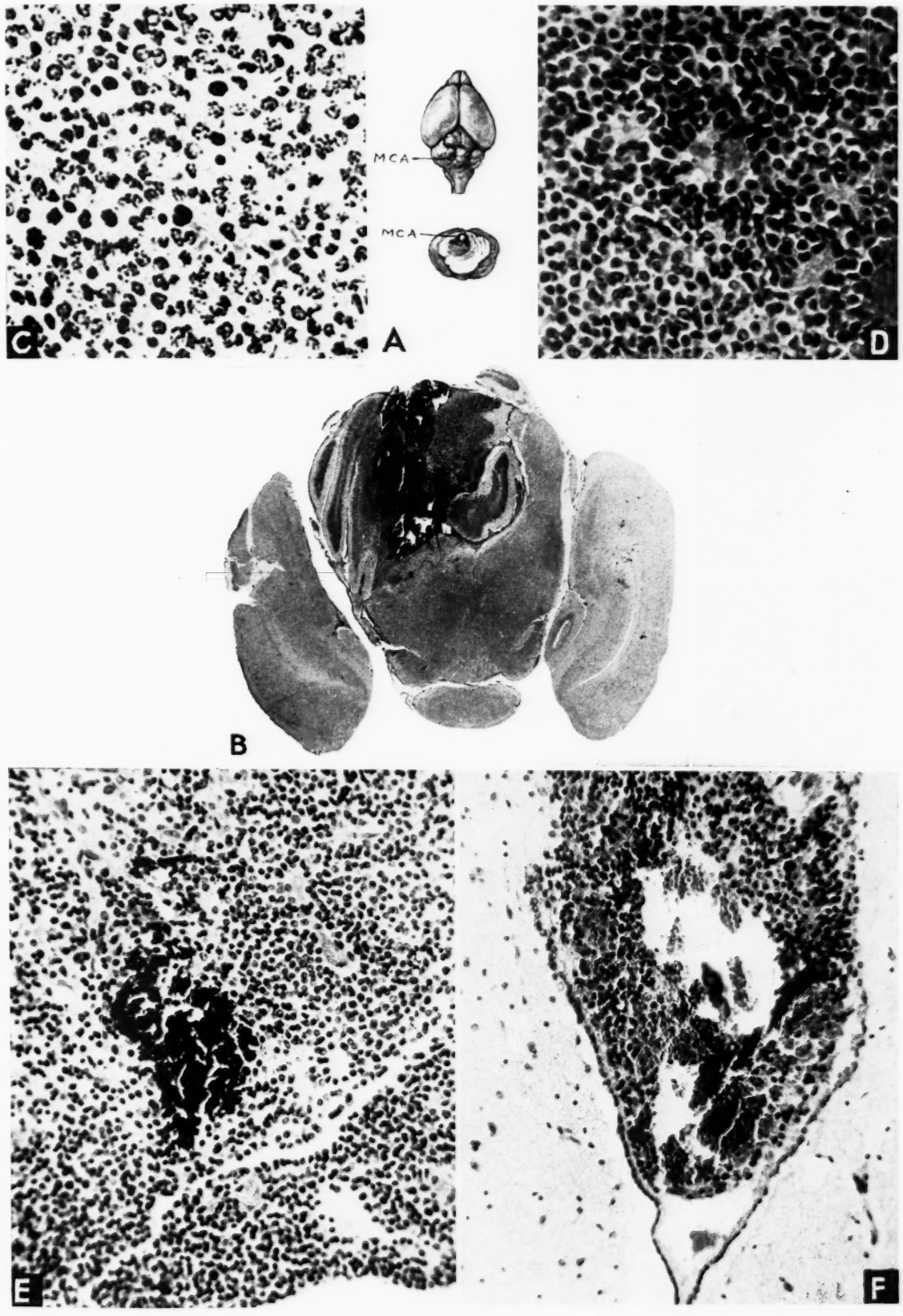

FIG. 3.—Mouse No. 52. Medulloblastoma. A. Drawing of tumor in cerebellum at site of carcinogen (MCA). B. Photomicrograph of neoplasm in cerebellum. H & E stain; mag. × 6. C. No reticulin fibers in tumor. Wilder stain; mag. × 450. D. Pseudorosette formed by tumor cells. H & E stain; mag. × 350. E. Calcium salt deposit in tumor. H & E stain; mag. × 350. F. Tumor invasion of aqueduct of Sylvius. H & E stain; mag. × 175.

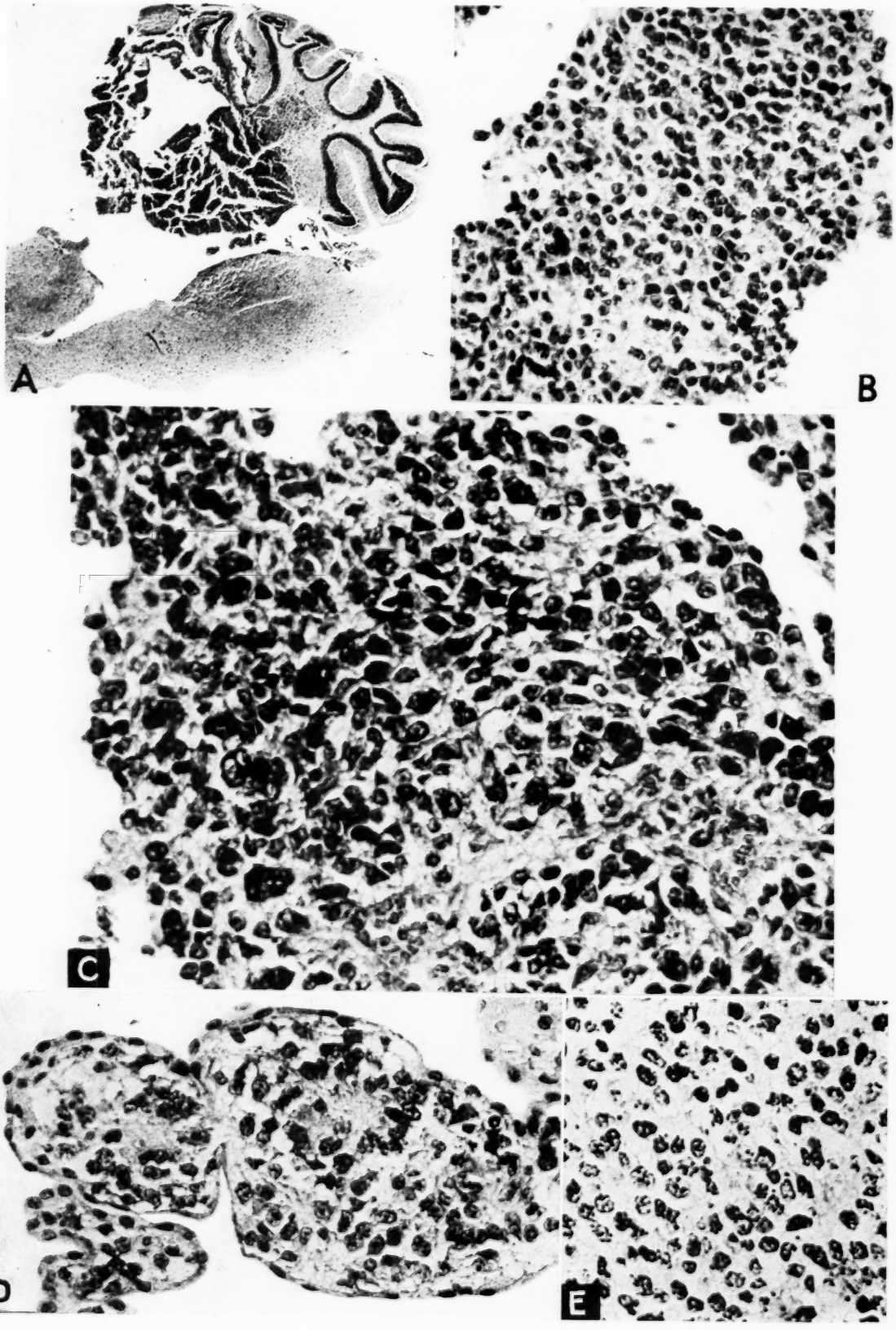

FIG. 4.—Mouse No. 49. Medulloblastoma. A. Tumor in left half of cerebellum containing empty pellet space. H & E stain; mag. × 9. B. Photomicrograph of tumor cells. H & E stain; mag. × 250. C. Higher magnification of same cells in indifferently stained stroma. H & E stain; mag. × 450. D. Infiltration of choroid plexus by tumor cells. H & E stain; mag. × 300. E. Note absence of mesodermal fibers in tumor stroma. Wilder stain; mag. × 450.

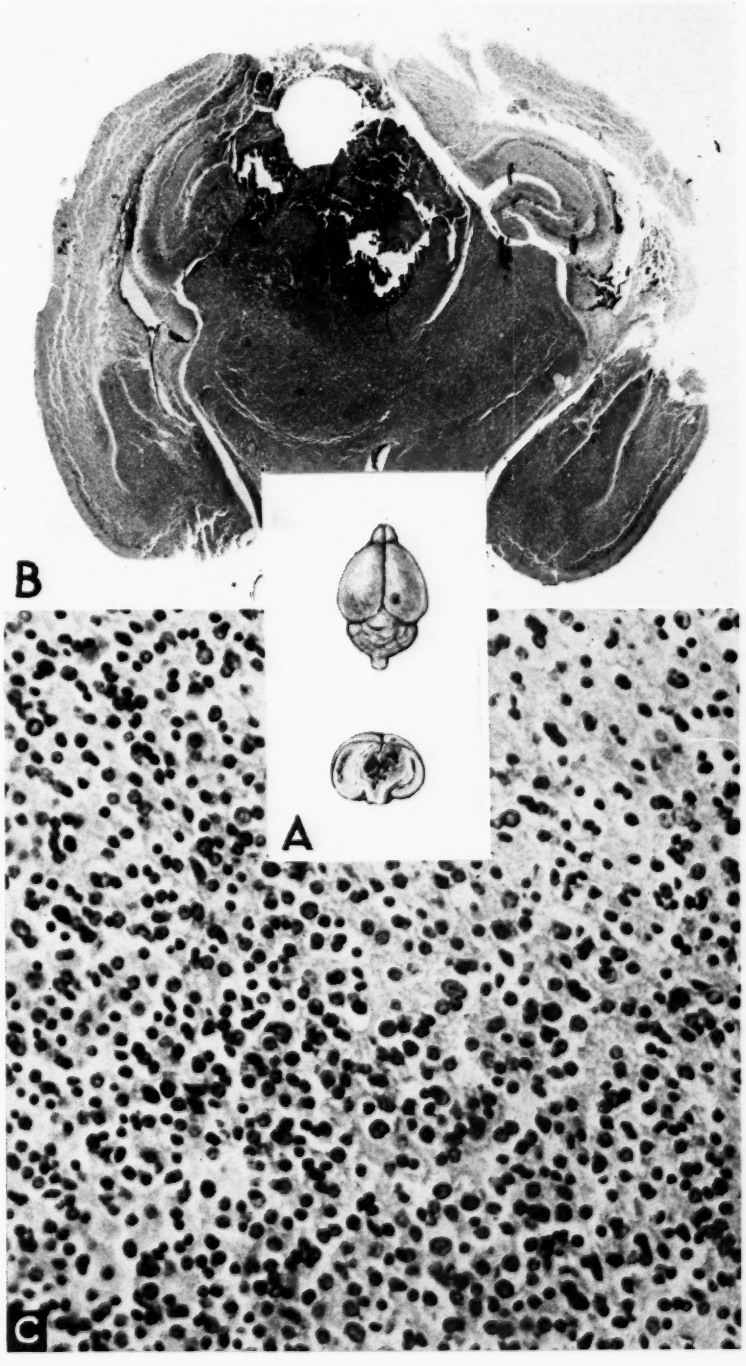

FIG. 5.—Mouse No. 16. Oligodendroglioma. A. Drawing of hemorrhagic tumor *in situ*. B. Note pellet space at top of infiltrating tumor which has shifted the midline to the left. H & E stain; mag. × 6. C. Note characteristic perinuclear halos in tumor cells. H & E stain; mag. × 400.

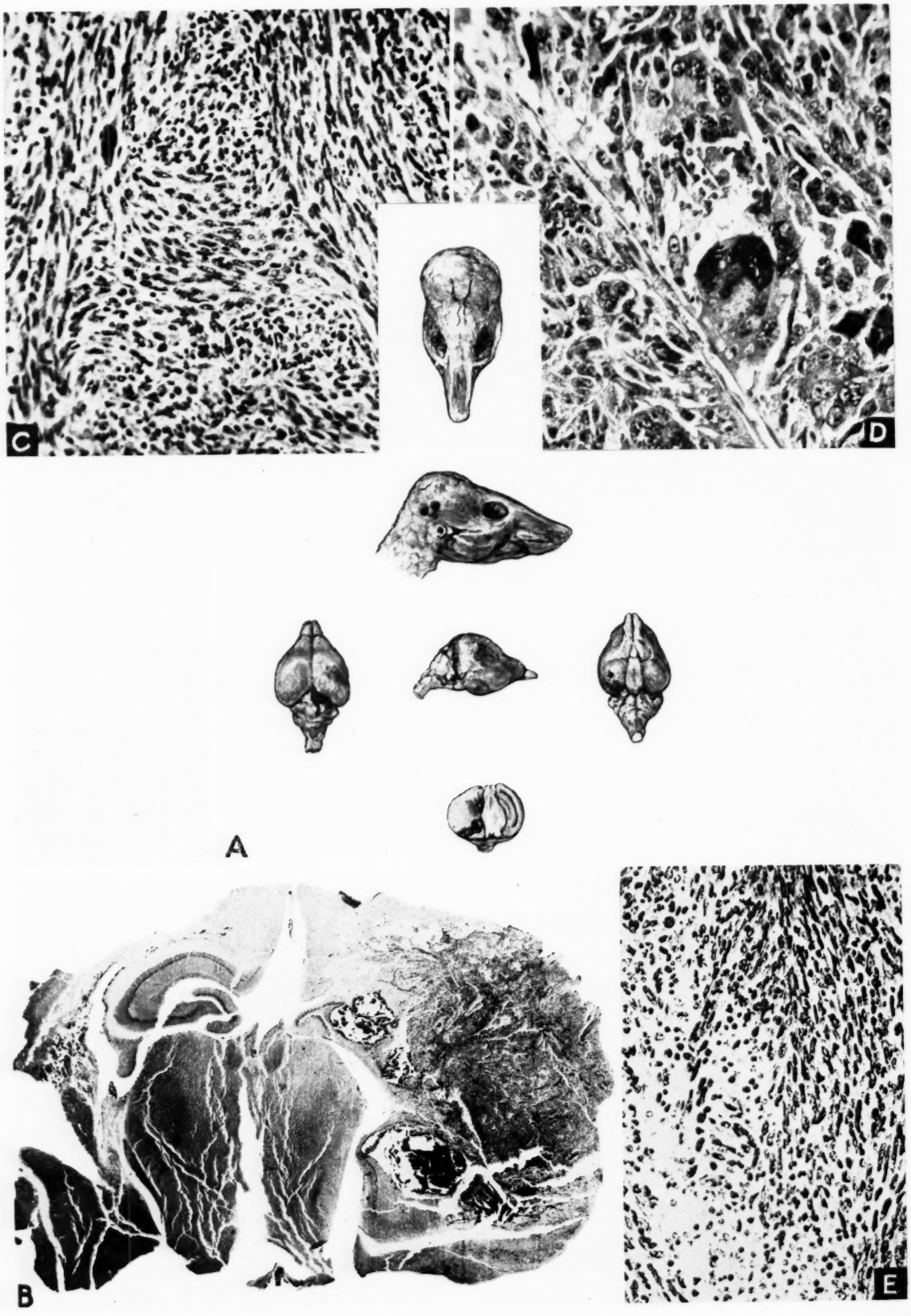

FIG. 6.—Mouse No. 55. Spongioblastoma polare. A. Note tumor mass replacing most of right cerebral hemisphere. B. The invasive neoplasm is seen in right hemisphere with hemorrhages on its margins. H & E stain; mag. × 5. C. Arrangement of spongioblasts in interlacing strands. H & E stain; mag. × 200. D. Multinucleated giant cells. H & E stain; mag. × 400. E. Note absence of reticulin fibers. Wilder stain; mag. × 200.

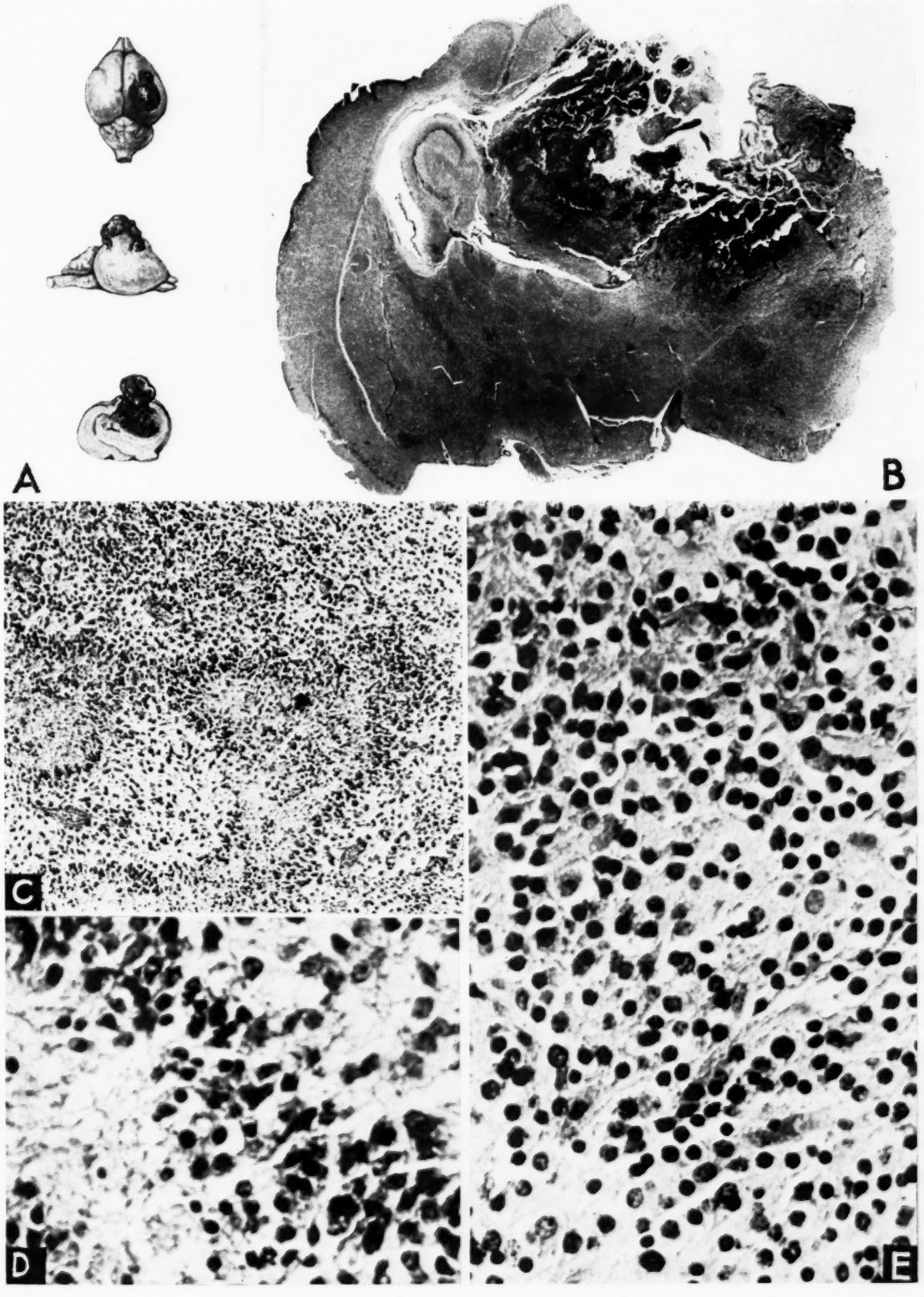

FIG. 7.—Mouse No. 11. Multiple gliomas. A. Drawing of tumor in right cerebral hemisphere. B. Note destruction of basal ganglia by neoplasm and shift of midline to left. H & E stain; mag. × 5. C. Pseudopalisade formation. H & E stain; mag. × 100. D. Spongioblasts under higher magnification. H & E stain; mag. × 400. E. Photomicrograph of oligodendroglioma portion of neoplasm. Note typical cells with perinuclear halos. H & E stain; mag. × 400.

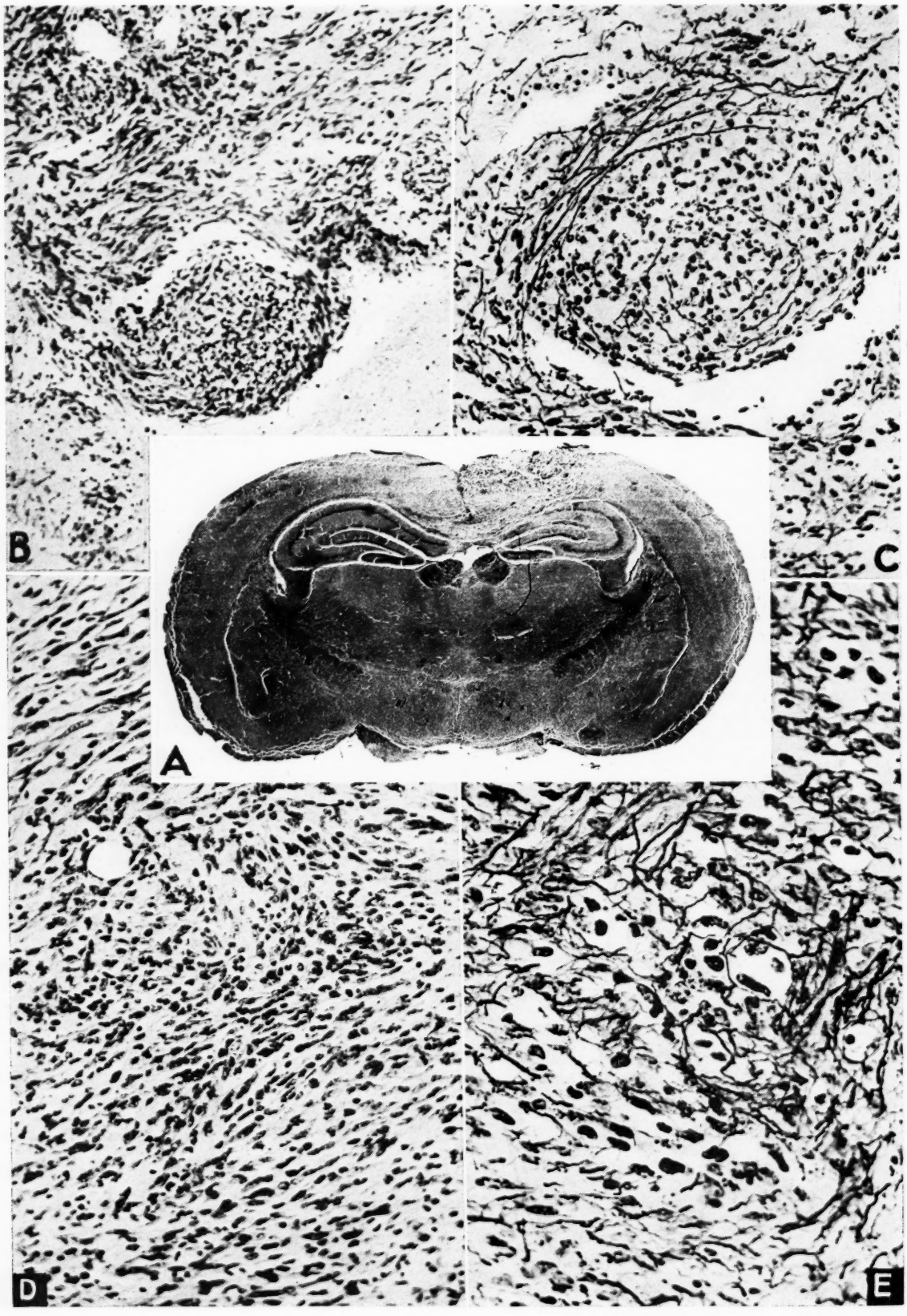

FIG. 8.—Mouse No. 83. Meningeal sarcoma. A. Loosely constructed neoplasm invading right parietal cortex near longitudinal fissure. H & E stain; mag. × 6. B. Whorl formation in tumor. H & E stain; mag. × 100. C. Reticulin in whorl. Wilder stain; mag. × 300. D. Interlacing bands of cells in subcutaneous transplant. H & E stain; mag. × 300. E. Abundant reticulin in transplant. Wilder stain; mag. × 300.

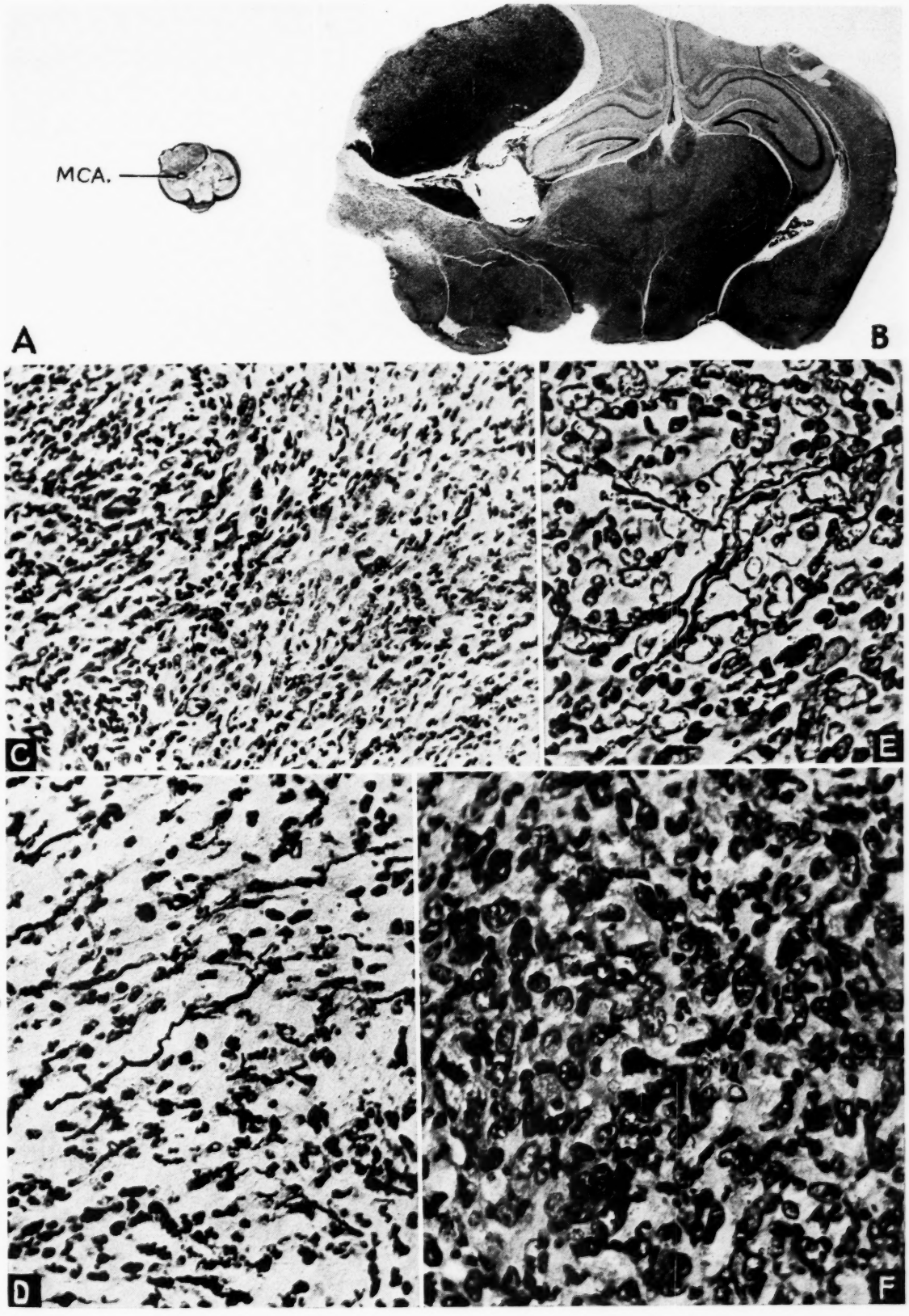

FIG. 9.—Mouse No. 10. Cerebral sarcoma. A. Drawing of sharply circumscribed tumor mass lying above carcinogen (MCA). B. Photomicrograph of neoplasm. Note empty pellet space. H & E stain; mag. × 5. C. Cellular detail of sarcoma. H & E stain; mag. × 300. D. Well impregnated reticulin fibers. Wilder stain; mag. × 500. E. Wilder preparation positive for reticulin in 1st transplant. Mag. × 600. F. Appearance of tumor in 1st transplant. Note cells in mitotic division. H & E stain; mag. × 300.

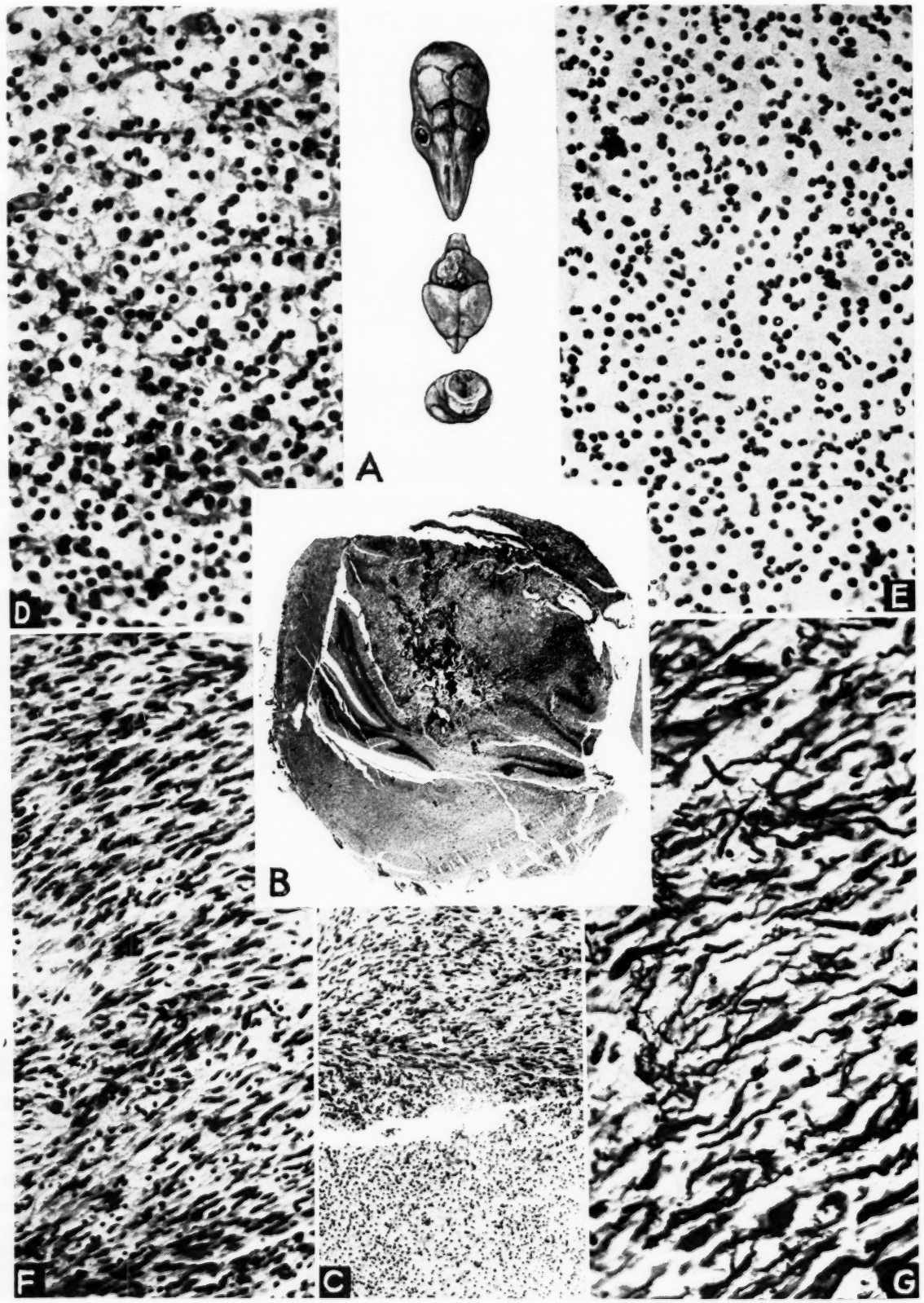

FIG. 10.—Mouse No. 44. Mixed sarcoma and glioma. A. Appearance of cerebellar neoplasm. Drawing. B. Bulk of tumor—oligodendroglioma. Note cap of sarcoma in right upper corner. H & E stain; mag. × 7. C. Sarcomatous portion in upper half and gliomatous in lower half of photomicrograph. H & E stain; mag. × 30. D. Cells of oligodendroglioma in larger portion of tumor. H & E stain; mag. × 150. E. Wilder preparation of same part of tumor to show absence of reticulin. Mag. × 150. F. Cellular detail of sarcomatous portion of tumor. H & E stain; mag. × 150. G. Wilder preparation of latter part of tumor to show abundant argyrophile fibers. Mag. × 150.

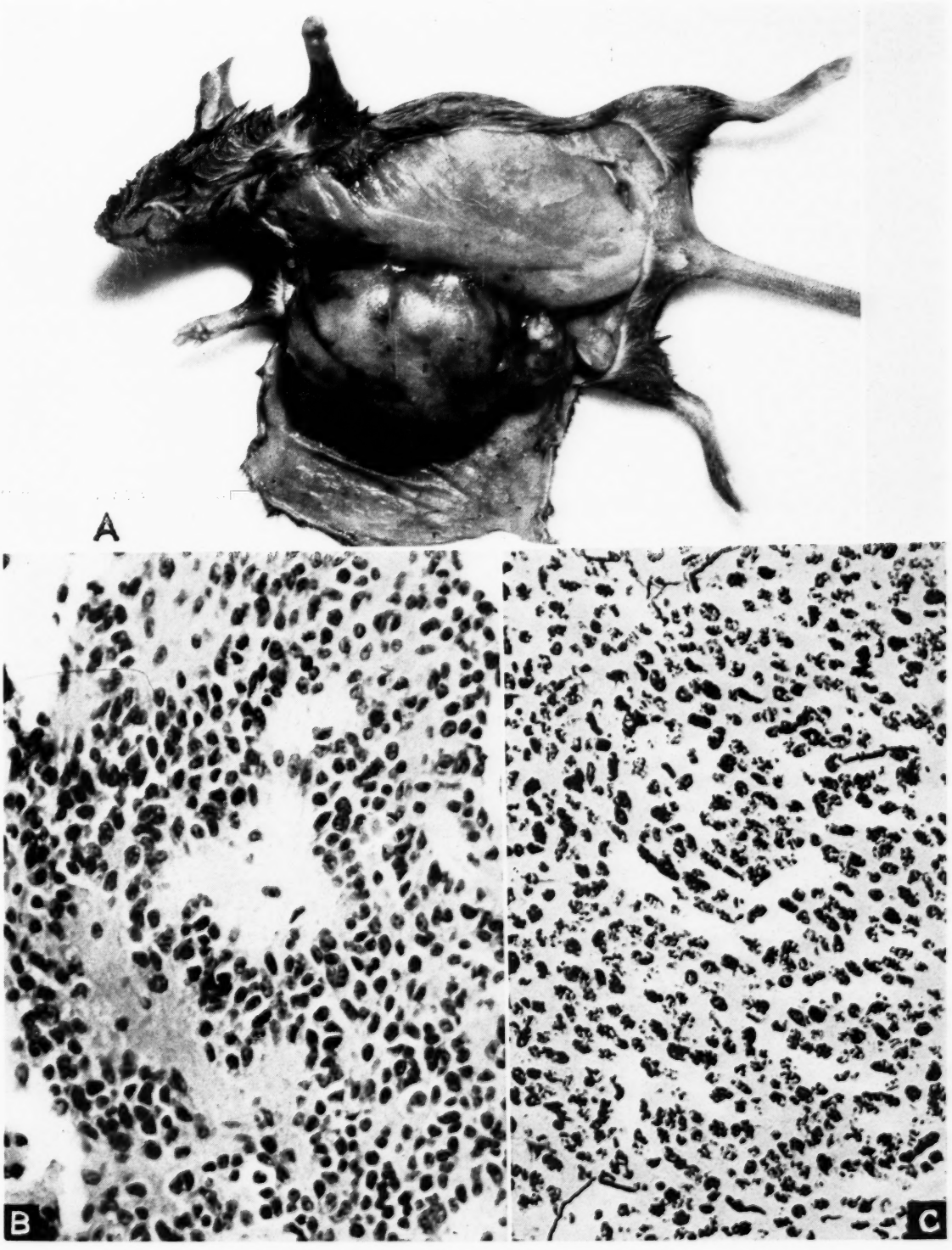

FIG. 11.—Mouse No. 49. Medulloblastoma. A. Tumor transplant in subcutaneous tissues. B. Pseudorosette in transplant. H & E stain; mag. × 400. C. Negative Wilder stain of same transplant. Mag. × 350.

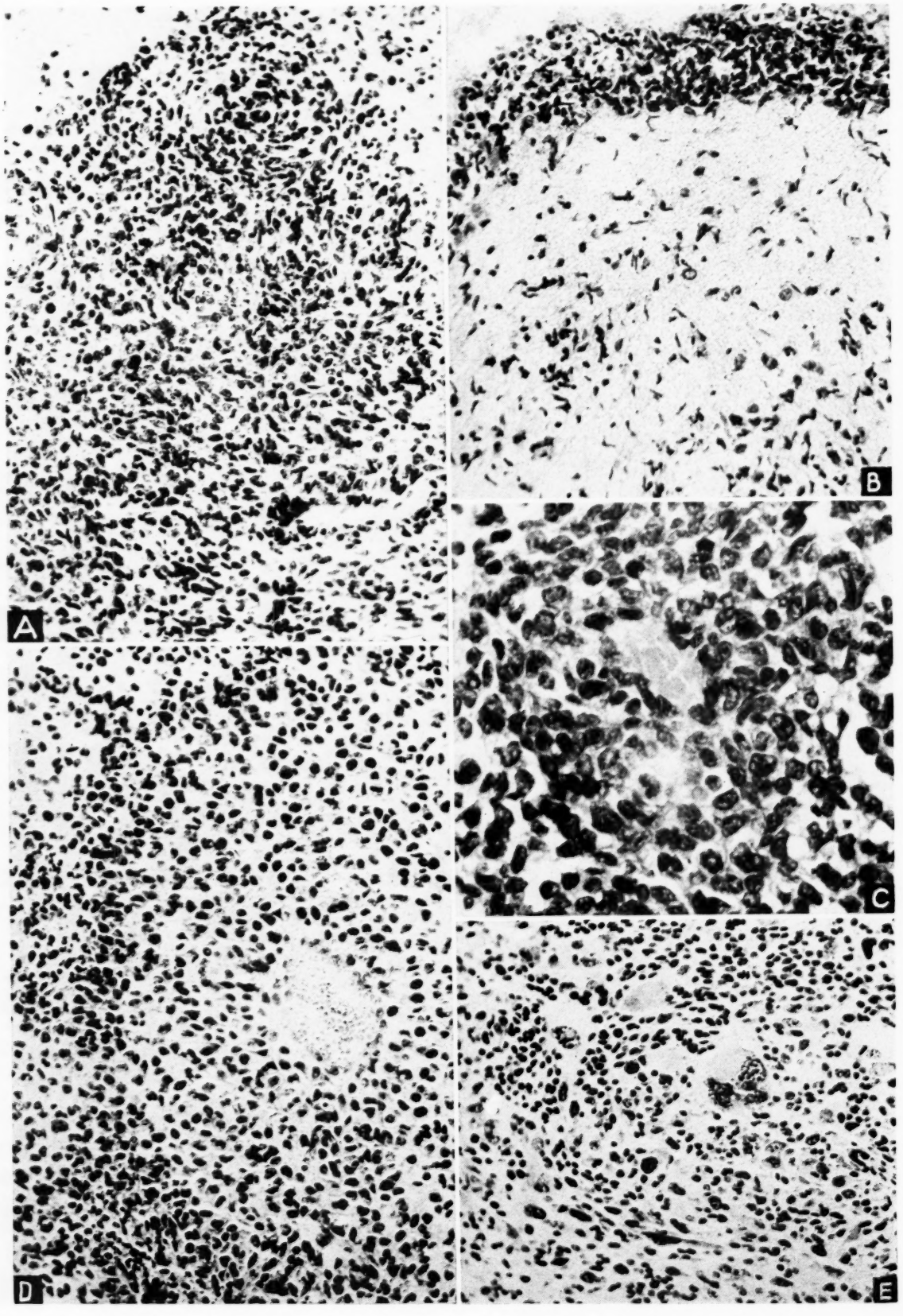

FIG. 12.—Mouse No. 74. Unclassified glioma. A. Microscopic appearance of original tumor in right parietal lobe. H & E stain; mag. × 300. B. Tumor cells infiltrating leptomeninges. H & E stain; mag. × 300. C. Pseudorosette formation of tumor cells in 1st transplant. H & E stain; mag. × 300. D. Tumor cells arranged around blood vessel in 11th transplant. Note epithelioid nature of cells. H & E stain; mag. × 300. E. Multinucleated giant cells in second transplant. H & E stain; mag. × 300.

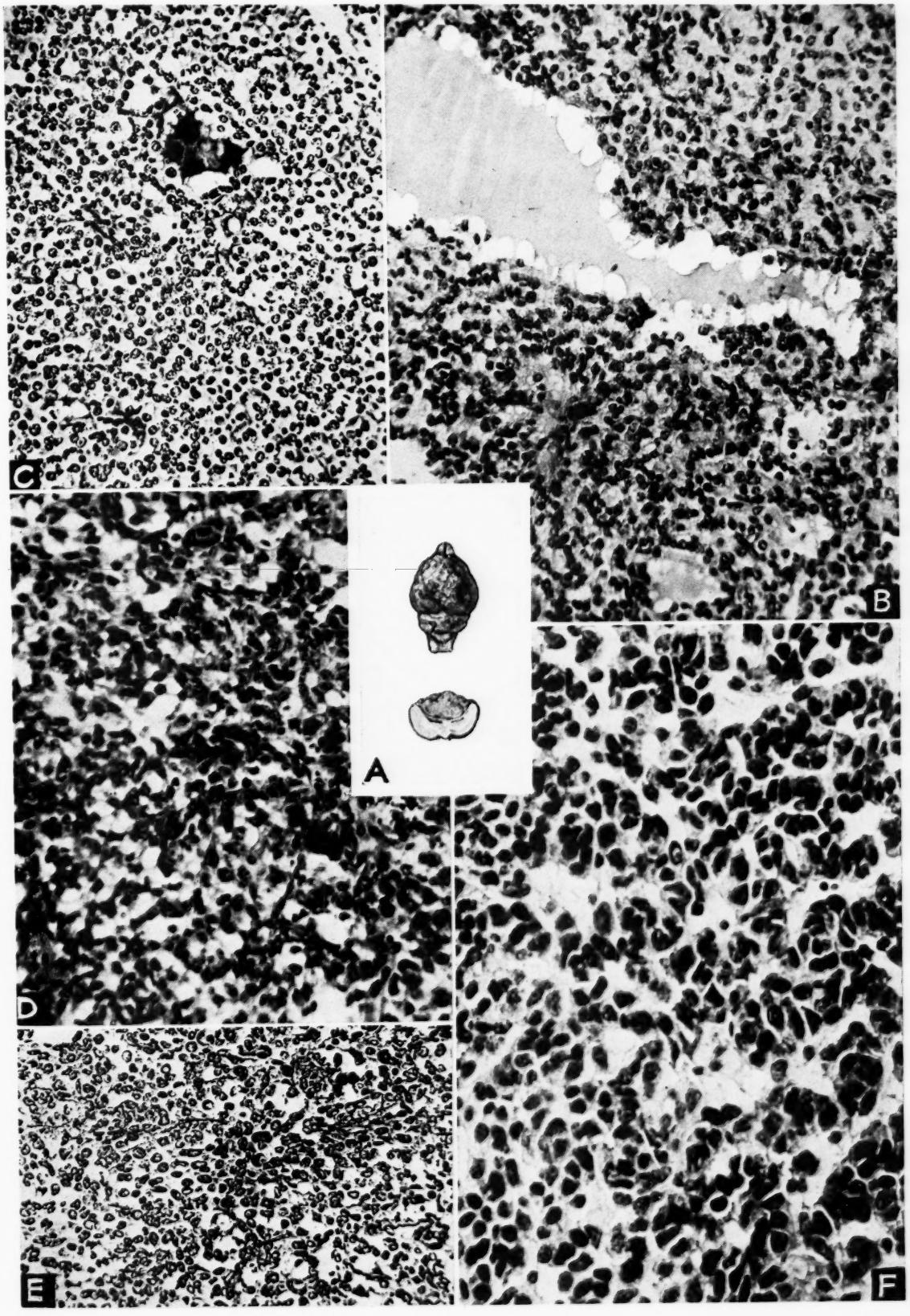

FIG. 13.—Mouse No. 69. Astrocytoma. A. Drawing of neoplasm in brain at site of carcinogen. B. Cystic spaces filled with colloid-like material. H & E stain; mag. × 200. C. Negative Wilder stain of same tumor. Mag. × 200. D. Appearance of tumor in 2nd transplant. H & E stain; mag. × 300. E. Note absence of reticulin in this transplant. Wilder stain; mag. × 300. F. Appearance of same tumor in 7th transplant. Note pseudorosette formations. H & E stain; mag. × 400.

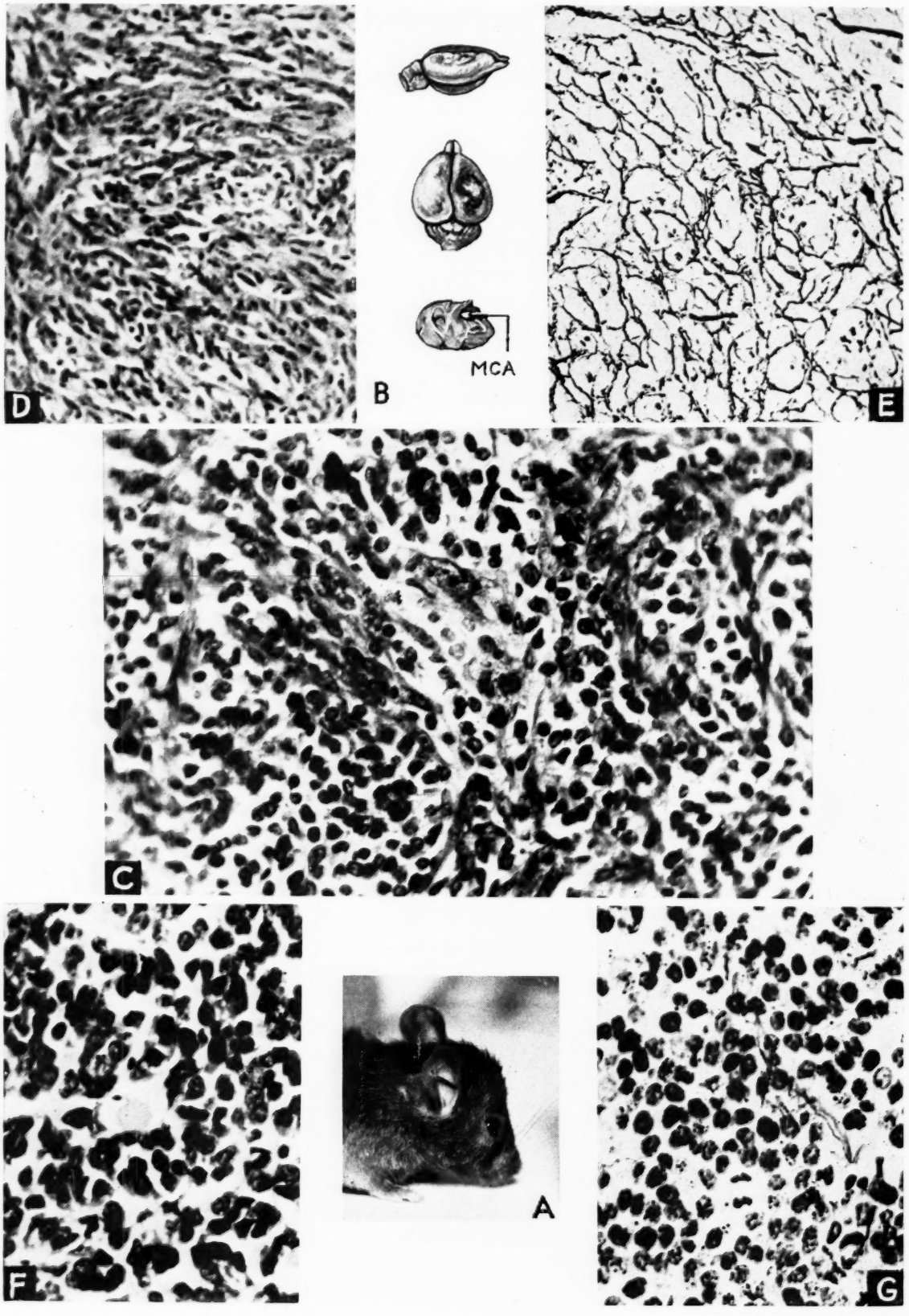

FIG. 14.—Mouse No. 106. Mixed sarcoma and glioma. A. Deformed head due to presentation of tumor beneath scalp through eroded calvarium. B. Drawing of tumor at site of carcinogen (MCA) in right cerebral hemisphere. C. Original tumor. Note mixture of spindle-shaped mesodermal elements and round gliogenous cells. H & E stain; mag. × 300. D. Sarcoma in mouse No. 5 of 1st transplant. H & E stain; mag. × 300. E. Same tumor in Wilder preparation. Note abundant reticulin. Mag. × 500. F. Glioma in mouse No. 3 of 2nd transplant. H & E stain; mag. × 300. G. Same tumor in Wilder preparation. Negative for reticulin. Mag. × 300.

Comparison of Methyl Salicylate and Benzene as Solvents for Methylcholanthrene*

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Among the many factors which may modify the action of carcinogens in the induction of tumors in mice, the agents in which the chemicals are carried must be considered. Because of its keratolytic properties and the facility of absorption through the intact skin, methyl salicylate was tested as a solvent for tumor-producing hydrocarbons. Methylcholanthrene was chosen as the carcinogen. A comparison was made of the carcinogenic activity of methylcholanthrene in methyl salicylate and in benzene. The criteria used for comparing the carcinogenic activities were the latent periods for papilloma formation and for the onset of malignant tumors as determined by progressive growth of nodules and microscopic postmortem examination.

Methods

Mice of 8 inbred strains were divided into 4 groups with nearly equal proportions of each strain in each group. Thirty-six were painted with methylcholanthrene in methyl salicylate, 25 with methylcholanthrene in benzene, 39 with methyl salicylate alone, and 25 with benzene alone. Five mgm. of methylcholanthrene were contained in 1 cc. of the solvent in each instance. The reagents were applied to the backs of the mice with a camel's hair brush at biweekly intervals. Although less exact than application from a syringe, this procedure was less lethal.[1] Treatment was continued for 400 days.

The time of appearance of the first papilloma and the time of beginning induration and formation of a subcutaneous mass were recorded. The subcutaneous tumors were excised, fixed in Bouin's fluid, and stained with hematoxylin and eosin in order to verify their nature.

Results

The average time from the first application of carcinogen to the appearance of papillomas was 160 days in the mice painted with methylcholanthrene in methyl salicylate (Table I). In those painted with methylcholanthrene in benzene this average time was 156 days. The average time between the beginning of treatment and the occurrence of malignant tumors was 214 days in the former group and 233 days in the latter. Of 28 mice living at the time of appearance of the first papilloma, 26 developed papillomas, and 22 eventually developed malignant tumors in the methylcholanthrene-methyl salicylate group. Of 25 mice painted with methylcholanthrene in benzene, 24 developed papillomas and 19 later developed malignancies. The average number of papillomas per individual was 2.8 in the first group and 2.3 in the second group. Malignant tumors arose at two sites in two cases in each group and at three loci in one mouse painted with methylcholanthrene in methyl salicylate. The tumors had coalesced in these mice before sections were taken. Both malignant tumors and papillomas arose in the general region painted. The former were usually infected and in many cases the mice were cachectic. The curves show the tumors occurring up to a given time calculated as a percentage of the number of mice alive at that time (Fig. 1).

Table I: Results of Painting Mice with Methylcholanthrene Dissolved in Methyl Salicylate or Benzene

Preparations	No. alive at 114 days *	Papillomas			Malignant tumors	
		No.	Average induction time in days	Average no. per mouse	No.	Average induction time in days
Methylcholanthrene in methyl salicylate	28	26	160	2.8	22	214
Methylcholanthrene in benzene	25	24	156	2.3	19	233
Methyl salicylate	28	0	...	...	0	...
Benzene	20	0	...	...	0	...

* Time of development of first papilloma.

* This investigation was supported by a grant from The International Cancer Research Foundation.

[1] Worthington (18) dropped an exact amount of methylcholanthrene in methyl salicylate on the dorsum of each of 50 mice of various inbred strains. Forty-nine of the mice died within the first 12 hours, apparently as a result of the toxicity of the methyl salicylate.

Five different types of tumors not including metastatic growths were found in mice receiving methylcholanthrene (Table II). One mammary adenocarcinoma was found in a CBAN female 139 days after the painting was begun. A papilloma occurred at 167 days in this animal. One extension to the pancreas and two metastases to the lung were observed. The tumors referred to as mixed in this paper are those in which two types of neoplastic tissue appear side by side in the microscopic sections. An interesting fact is that eosinophils, in which the nucleus was not lobed, sometimes appearing almost like that of a plasma cell, were found in all but three mice painted with methylcholanthrene in methyl salicylate and in all but one mouse painted with methylcholanthrene in benzene. In some cases the tissue eosinophilia was exceptionally pronounced, most of the cells appearing in the edematous corium, but some in the tumor tissue itself.

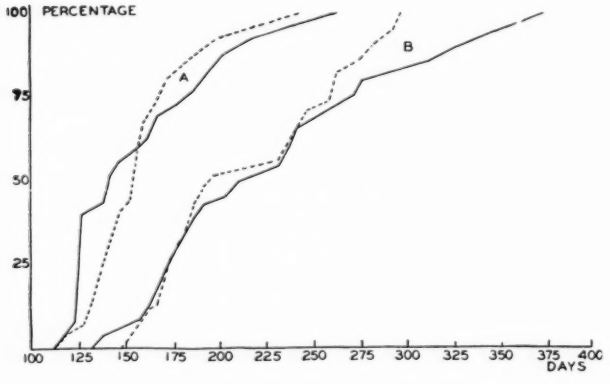

FIG. 1.—Graph showing the time from the beginning of treatment to the appearance of (A) papillomas and (B) malignant tumors. Continuous line—methylcholanthrene dissolved in benzene; dotted line—methylcholanthrene dissolved in methyl salicylate.

No tumor appeared in the mice painted with benzene or with methyl salicylate alone. These animals were treated for 400 days. At this time all mice painted with methylcholanthrene in one solvent or the other had either developed tumors or had died. Ten mice painted with methylcholanthrene in methyl salicylate died without developing papillomas or subcutaneous tumors. Eight of these died before the first papilloma appeared in the group. Only one mouse painted with methylcholanthrene in benzene failed to exhibit a papilloma, but this animal developed a malignant neoplasm.

DISCUSSION

In considering the effect of solvents for carcinogens (6, 13) discussion is confined to those papers in which authors have specifically tested the solvents under similar laboratory conditions.

Berenblum and Kendal (4) found that mice showed more tumors when dibenzanthracene in colloidal solution was injected intraperitoneally than when injected in lard. On the other hand, Oberling and co-authors (10) found fewer tumors in mice injected with benzpyrene in the colloidal state than with the carcinogen in olive oil. Also Andervont and Lorenz (1) found that subcutaneous tumors appeared less rapidly when dibenzanthracene was injected dispersed in horse or dog serum than when injected in solution in lard. Tumors occurred more rapidly when dibenzanthracene dispersed in horse serum with added charcoal was injected subcutaneously in C3H mice than when a dispersion in horse serum alone was used (2).

Peacock (11) found that dibenzanthracene in lard evoked tumors in approximately 50 per cent of the fowls injected, whereas no tumors occurred when chicken fat was used as the solvent. In a continuation of the work, Peacock and Beck (11) found that fewer tumors occurred when benzpyrene was injected subcutaneously in mouse fat, ether, or in the powdered form than when the solvent used was olive oil, mouse lipoids, or a $\frac{2}{3}$ olive oil and $\frac{1}{3}$ paraffin mixture. Morton and Mider (9) substantiated this work in experiments on mice of the C57 strain, using a petroleum ether extract of mouse carcasses. However, Oberling *et al.* (10) found no difference in tumor incidence when rat fat, lard, and olive oil were used as solvents for benzpyrene injected into white rats. Also Shimkin and Andervont (14) obtained no significant results in testing the possible inhibition of tumor formation by extracts of mouse tissue as solvents for dibenzanthracene and methylcholanthrene.

A difference in the potency of the carcinogen when dissolved in different solvents has been reported for oleic acid compared to liquid paraffin by Twort and Bottomley (15), oleic acid compared to chloroform by Twort and Twort (16), benzene compared to liquid paraffin and ether by Crabtree (7), for various lots of lard and a group of glycerides and esters compared by Shimkin and Andervont (14), and for certain fractions of creosote oil when compared by Shear and co-workers (12).

Berenblum and Kendal (4) and Peacock and Beck (11) found that groups of mice in which the carcinogen was retained at the site of injection longest developed more tumors. The effect of carcinogens is not only altered by the medium in which they are carried but also by application of various media to the skin at other times (15, 17). In some cases tumors have appeared when the solvents alone have been used (3, 5, 8, 11, 15).

From the data presented, it is apparent that the latent period of papillomas and malignant tumors is not different when methyl salicylate is used as a solvent for methylcholanthrene as compared to methylcholanthrene in benzene (Table I and Fig. 1). The types of malignant tumors induced in each group are not

TABLE II: TYPES OF TUMORS RESULTING FROM PAINTING WITH METHYLCHOLANTHRENE IN DIFFERENT SOLVENTS

Solution used	Epidermoid carcinoma	Spindle cell sarcoma	Mammary adeno-carcinoma	Mixed tumors: Epidermoid and basal cell carcinoma	Mixed tumors: Epidermoid carcinoma and spindle cell sarcoma	Metastases	Total
Methylcholanthrene in methyl salicylate	12	0	0	1	3	3	16
Methylcholanthrene in benzene	11	3	1	0	1	0	16

greatly different in the two groups especially when one considers separately the types of tumor tissue found in the mixed tumors (Table II). For instance, there were 3 tumors containing spindle cell sarcoma in the methylcholanthrene-methyl salicylate-treated animals and 4 such tumors in animals treated with methylcholanthrene in benzene. The average number of papillomas in the two groups differs by only 0.5. Both groups contained mice in which malignancies arose from more than one site.

It is possible that a difference could be detected if smaller doses of methylcholanthrene had been applied, since the amount used may have been so overwhelming as to mask any effect of the solvent, methyl salicylate, as compared to benzene. It has been suggested in the literature (12) that lower levels of carcinogen would be required for such an effect to be detected.

Summary

Under the conditions of this experiment no difference was found in the tumor incidence, type, and time of appearance in mice painted biweekly with methylcholanthrene in methyl salicylate and methylcholanthrene in benzene.

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Comparison of Methylcholanthrene Hyperplastic Epidermis with Benign Hyperplastic Epidermis in Healing Wounds*

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It is highly desirable to be able to recognize lesions likely to develop into cancer. One reason for so much difference of opinion is that the problem has not been clarified by experimental work on animals. A major research project in the Barnard Free Skin and Cancer Hospital is the integration of changes that occur in epidermal methylcholanthrene carcinogenesis of mice.

Epidermis, rendered hyperplastic by methylcholanthrene, will, after a sufficient number of properly spaced paintings in the right concentration, give rise to squamous cell carcinomas in a fairly high percentage of cases. Consequently it may be assumed that it has been rendered more surely precancerous than any lesion naturally occurring in the human body. The other desideratum is to create for comparison another epidermal hyperplasia of equal thickness in mice which is not precancerous. This can easily be done by excising small pieces of skin and by selecting the regenerating epithelial edges. Since these experimental conditions afford ample opportunity for the comparison of precancerous and regenerative (benign) epidermal hyperplasia, an intensive search has been commenced for differences between them. We think that in this way we are likely to be able to detect in the hyperplasia the essential precancerous modifications.

The literature on precancerous lesions is enormous. Dubreuilh (8) was the first to use the term "precancerous" in his thesis at the Third International Dermatological Congress in London in 1896. He applied the term to a group of skin conditions that were likely to become malignant.

Darier (7) employed the word "dyskeratoses" to indicate individual differences between cells in the epidermis which had undergone atypical evolution leading to precocious and imperfect cornification. The four conditions he called dyskeratoses were Darier's disease, molluscum contagiosum, Paget's disease, and Bowen's disease. His use of the term indicated that he considered the dyskeratoses precancerous. Masson (19), Pautrier and Archambault (22), and Kogoj (15) were of different opinions and considered the "dyskeratoses" entirely different diseases with nothing in common and not all precancerous. McCarthy (20) stated that as all dyskeratoses are not precancerous, all precancerous lesions are not necessarily of a dyskeratotic nature. Satenstein (23) made use of the qualifications "accelerated" and "retarded" for the types of keratinization to distinguish between benign and malignant dyskeratoses.

Montgomery (21) employs the phrase "individual cell keratinization" to describe the phenomenon of malignant dyskeratosis of individual cells of the epidermis as seen most clearly in Bowen's disease. He listed as "precancerous dermatoses": Bowen's disease, senile keratosis, keratosis resulting from arsenic, tar, radiation, and various forms of leukoplakia of mucous membrane of the mouth and genitalia. He found that 20 per cent or more of cases of all these conditions develop epithelioma of squamous cell type. Taussig (29) observed 39 of 76 cases of vulvar cancer to be associated with leukoplakia, or approximately 50 per cent.

Freudenthal (10), Hookey (13), and Bloch (1) have enumerated the principal histopathologic changes in hyperkeratosis senilis and verruca senilis, a combination of which is to a certain degree typical of precancerous affection. They are irregular epithelial proliferation, irregularities and unrest in the cell structure, atypical and polymorphous cells and nuclei, pathological mitoses and amitotic figures, dyskeratotic manifestations and reactive inflammation in the adjacent parts of the cutis.

Ewing (9) has stated that, "The theoretical distinctions which a general survey establishes between neoplastic and inflammatory hyperplasia are sharp and fundamental, but these distinctions fail us when we have to search for them in processes of doubtful nature. Here we assume them to exist from our general knowledge but we cannot prove their presence."

In the characterization of precancerous lesions clinical data have been supplemented by morphological data derived chiefly from the microscopic examination of sections prepared by the usual routine methods. In consideration of the great importance of the problem, it is surprising to find that information bearing on the physicochemical properties of the lesions and on their physiological properties is conspicuous by its absence. As Cowdry (4) has indicated, workers have perhaps thought the effort futile as long as it is so difficult to mention a property of malignant cells altogether absent in their normal prototypes. In this paper we have made an attempt to fortify morphological data by an investigation of displaceability under ultracentrifugal force and of mineral constituents by microincineration.

Material and Methods

Specimens of hyperplastic epidermis in a series of New Buffalo mice were selected. These mice were

* This investigation was aided by grants from The Jane Coffin Childs Memorial Fund for Medical Research and from The National Cancer Institute.

treated with 0.6 per cent methylcholanthrene in benzene 3 times a week. The carcinogen was applied uniformly with a small brush to an area about 5 mm. in diameter at the back of the neck. A single specimen on each of the following days after the beginning of treatment was studied: 11, 18, 22, 25, 39, 43, 46, 49, 51, and 64 days.

The mice used for induction of benign epidermal hyperplasia were of mixed stock. At first we tried to work with scarlet red in olive oil because we felt sure that the resulting hyperplasia would certainly not lead to the development of cancer (Seelig, Eckert, and Cooper, 27).

A saturated solution of scarlet red in olive oil was applied to the epilated skin surface of 22 mice 6 days a week for 150 days, but no hyperplasia of sufficient extent for comparison was obtained. Another group of 23 mice was treated in the same way except that every 10 days in the first 50 days the area treated was gently scratched with a scalpel in two directions at right angles. Again the hyperplasia was unsatisfactory.

Suitable material was, however, collected from two other groups of mice. In the first, consisting of 31 mice, the hair was removed from a small area on the back of the neck with sodium sulfide. A day later about 1.5 sq. cm. of skin, full thickness, was excised and the open wounds were allowed to heal without any treatment. The very few wounds that became infected were not used for material. Tissues were removed from 6 mice after 10 days and from 11 others after 14 days.

In the second group of 51 mice similar wounds were made and saturated scarlet red in olive oil was applied to each 6 days a week. Again infected wounds were rare and were not included in this study. Specimens were excised: 6 after 10 days, 4 after 17, and 14 after 19 days.

For histological comparison of the methylcholanthrene hyperplasia and the benign regenerative hyperplasia, tissues were routinely fixed in Bouin's fluid and paraffin sections, 5 microns in thickness, were stained with hematoxylin and eosin.

The displaceability of nuclear contents was determined by ultracentrifugation as described in an earlier paper by Cowdry and Paletta (5). All tissues were centrifuged in Locke's solution in a Beams type of centrifuge, driven by oxygen pressure of 60 lbs. per sq. inch, yielding a displacing force of approximately 350,000 times gravity, operating for 30 minutes. Some of the specimens described in the above-mentioned paper were used to compare with benign hyperplasia of healing wounds. Parts of 17 healing wounds (benign hyperplasias) were centrifuged.

Scott's (24) method of microincineration was employed for mineral constituents. Twenty methylcholanthrene hyperplasias and 19 benign hyperplasias from the wounds were incinerated. First, a few sections from a methylcholanthrene hyperplasia (M. H.) were mounted on a slide and after them on the same slide were mounted some sections from a benign hyperplasia (B. H.). But in all the later work a better comparison was provided by mounting the methylcholanthrene and benign hyperplasia sections alternately: M. H., B. H., M. H., B. H., etc.

Observations

Two reservations are necessary with respect to the precancerous condition of epidermis made hyperplastic with methylcholanthrene:

1. Since we have not determined by experiment the percentage of epidermis which would eventually yield carcinomas if the treatment specified were stopped after 11 days and the animals continued to live, it is unsafe to call an 11-day hyperplasia precancerous. The chances that cancer would have developed if the tissues had not been biopsied increase with the duration of methylcholanthrene treatment. Specimens of 40 days and more are much more likely to be precancerous at the time of examination. On the other hand, it is unsafe to assume that even after brief treatment the hyperplastic epidermis has not been modified in the direction of cancer formation because the Tworts (30) have found that "cells rendered abnormal by a few applications of benzpyrene quickly pass into the irreversibly cancerous phase when stimulated with oleic acid."

2. Because the malignant change takes place in sharply limited foci within the areas treated and not evenly throughout their extent, it cannot be stated that *all* of the hyperplastic epidermal tissue in any of the areas, even after prolonged treatment, is precancerous. Yet it is possible that, although the malignant changes begin in small foci within the areas, the remaining parts of the areas have nevertheless been rendered potentially precancerous by the methylcholanthrene. MacKenzie and Rous (18) have observed that "A carcinogenic tar applied to rabbit skin renders many more epidermal cells neoplastic than ever declare themselves by forming tumors." They note, however, the curious fact that, in contrast to rabbits, no growths appeared during the healing of holes punched in mouse ears treated by carcinogens.

Parts of the epidermis from which cells were invading the underlying dermis were themselves considered cancerous and were of course excluded from this comparison. We are well aware that some lesions listed arbitrarily in this way as precancerous might be regarded by others as cancerous since they may resemble, for instance, the carcinoma *in situ* of Broders (2). Portions of hair follicles extending into the dermis were also excluded. Only the epidermis forming the

surface of the skin and surrounding the openings from which the hairs formerly projected was included.

In the case of the healing wounds care was also taken in the selection of hyperplastic epidermis though none of it could be considered precancerous. The thin sheet of epidermal cells beginning to cover the exposed surface of underlying tissue was excluded. The comparison was usually limited to the area of the original epidermis surrounding the excised tissue for a distance of about 6 mm. In this the number of layers of epidermal cells was increased by benign hyperplasia from the normal of 2 or 3 to from 10 to 14. It had attained approximately the same thickness as the methylcholanthrene hyperplastic areas of epidermis.

Structure.—Methylcholanthrene hyperplasia is often characterized by diversity of structure as compared with the uniformity of structure of the benign hyperplasia. Marked variation occurs in the size of the nuclei of basal cells after treatment with methylcholanthrene over a period of 18 days, which is earlier than such a variation is usually found (Fig. 1). A variation of this magnitude was not observed in benign hyperplasia (Figs. 5 and 6).

Fig. 2 shows a not unusual degree of nuclear hyperchromatism and enlargement of nucleoli in methylcholanthrene hyperplasia (25 days). In benign hyperplasia the nuclei may stain intensely and the nucleoli may be prominent but seldom to the same extent.

Figs. 3 and 4 are of different areas in the same, probably precancerous, specimen (46 days). The first represents a degree of irregularity of growth not observed in any of the benign hyperplasias and the second a uniformity of growth not suggestive of precancer. But in this second specimen the nuclei are large and there are many mitoses. The highest incidence of mitosis is in the area showing the least departure from typical cell shape. It is possible that the irregular growth appears not in an area of hyperplasia but in one in which for a time mitosis has not been frequent.

In the benign hyperplasia there is also regional diversity of structure but this depends upon the distance from the healing wound. At a given distance uniformity in structure is very definite. Benign hyperplasia at a distance of about 2 to 3 mm. from the margin of the excised area, 19 days after the excision, is represented in Fig. 5. In it there is greater uniformity in cellular size and structure than in any of the methylcholanthrene hyperplasias illustrated except that shown in Fig. 4. The intercellular spaces are less marked than in Figs. 1, 2, and 4 of methylcholanthrene hyperplasia, indicating less edema.

Benign hyperplasia within 1 mm. of the margin of the excised area is shown in Fig. 6. In this region, much nearer the excision than Fig. 5, there is extensive intercellular and intracellular edema far greater than that observed in any of the methylcholanthrene hyperplasias. It will be noted that the width of the intercellular spaces is often twice that of those in Figs. 1, 2, and 4, and that the intercellular bridges (spines) have been stretched considerably and their number decreased since some have probably been broken. The edema is greater proximally (near the basement membrane) than distally, as is to be expected because the blood vessels are proximal. There is fair uniformity in cell size and shape.

Other histological differences between methylcholanthrene and benign hyperplasia in our series, include in the former: (a) a more definite basement membrane with greater tendency to bulge into the dermis; (b) more acanthosis and less affinity of spinous cells for eosin; (c) less leucocytic infiltration than that at the edge of the wound; and (d) more prominent granular layer and slightly more hyperkeratosis.

Intranuclear viscosity.—The displacement by ultracentrifugal force of nuclear contents in a methylcholanthrene hyperplasia of 11 days is shown in Fig. 7. The force is from above downwards. In most of those nuclei which are cut approximately through their greatest diameters, the nucleoli and basophilic chromatin have shifted in a centrifugal direction—a phenomenon not observed by Cowdry and Paletta (5) in untreated, normal epidermis. Judging by the uniformity of the shift in the small area represented, the intranuclear viscosity of the majority of the cells is about the same. Those included in the photomicrograph are of the spinous variety. No basal cells are included, but

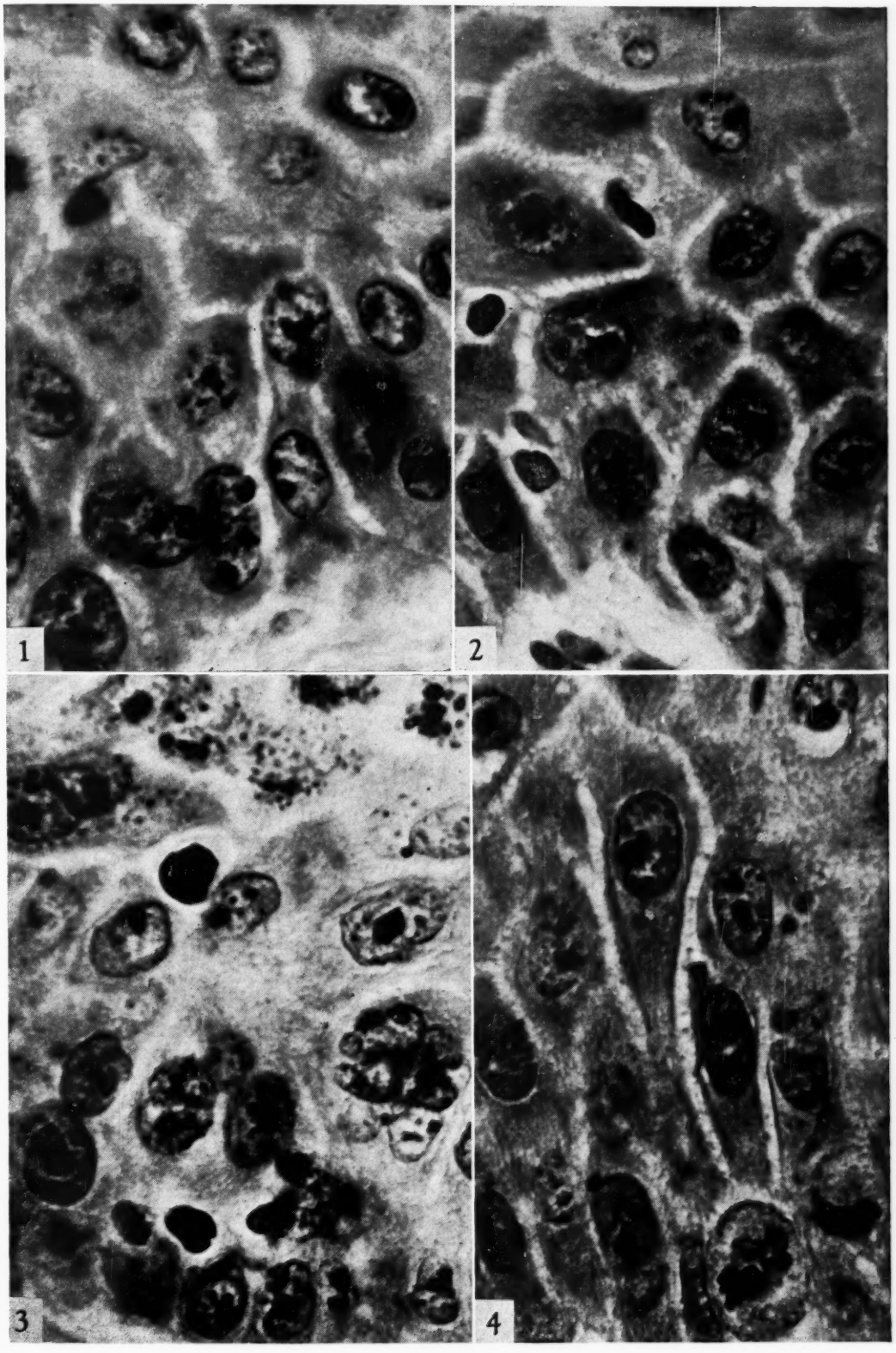
DESCRIPTION OF FIGURES 1 TO 4

FIG. 1.—Methylcholanthrene hyperplasia of epidermis (18 days) in New Buffalo mouse. Note the irregularity in cell size in the basal layer; the large basal nuclei, hyperchromatic on the left side. Hematoxylin and eosin stain. Mag. × 1040.

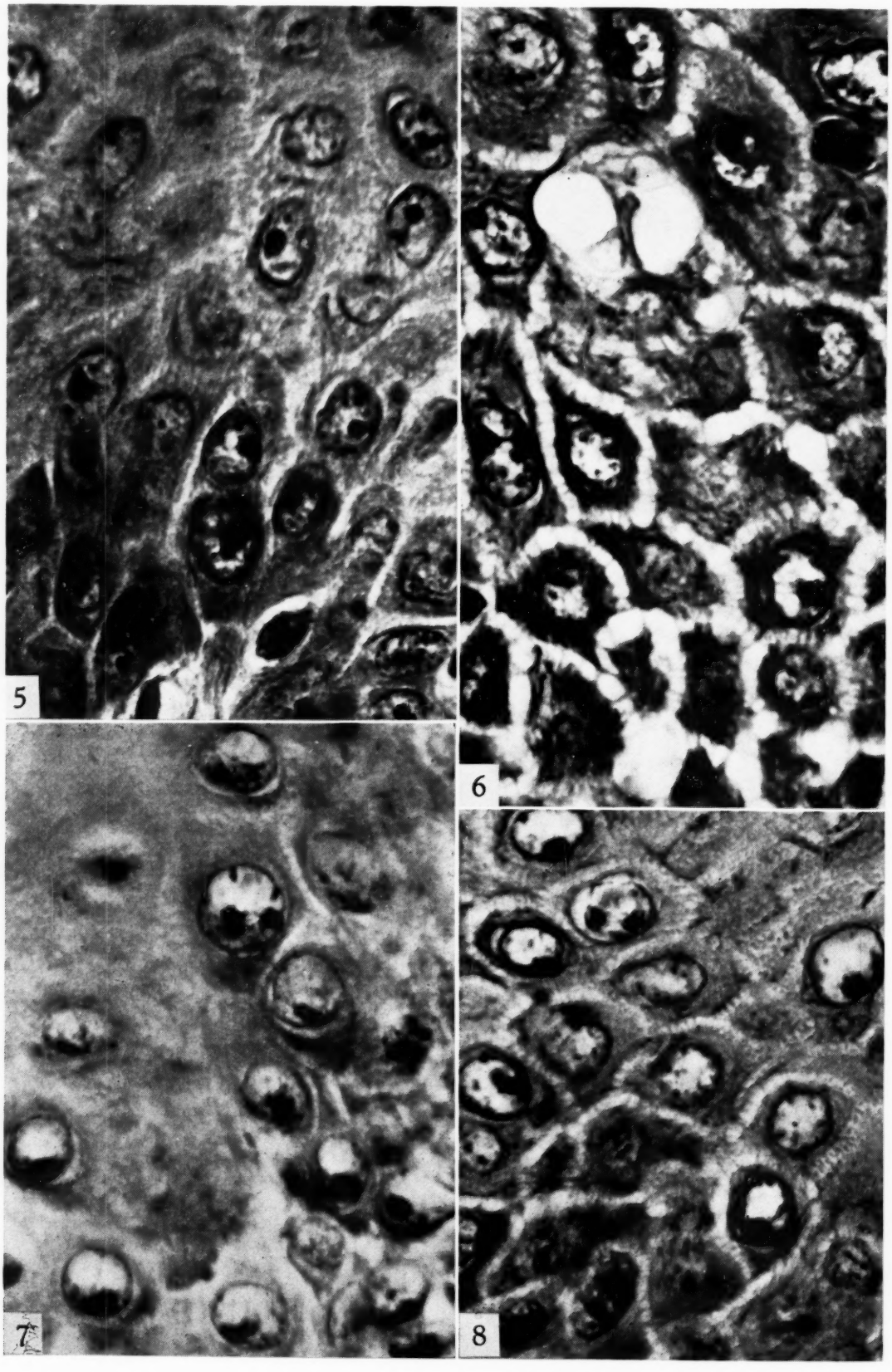
FIG. 2.—Methylcholanthrene hyperplasia of epidermis (25 days) in New Buffalo mouse. Observe the large nuclei with large nucleoli and hyperchromatism in basal and suprabasal layer. Hematoxylin and eosin stain. Mag. × 1040.

FIG. 3.—Methylcholanthrene hyperplasia of epidermis (46 days) in New Buffalo mouse. Small multinucleated cells in both spinous and granular layer; marked irregularity in cellular growth in spinous layer; large granular cells. Hematoxylin and eosin stain. Mag. × 1040.

FIG. 4.—Methylcholanthrene hyperplasia of epidermis (46 days) in New Buffalo mouse. Different area in same specimen as Fig. 3. Note the large columnar and pyramidal type of cells; many mitotic figures in basal layer (a more organized cellular growth). Hematoxylin and eosin stain. Mag. × 1040.



FIGS. 1 to 4.



FIGS. 5 to 8.

the spinous cells at the lower right corner are smaller than the others and not far removed in their properties or topographically from basal cells. In two or three cells the centrifugal cytoplasm stains more intensely and appears to be denser than the centripetal cytoplasm. The spinous cells involved do not exhibit either the hyperchromatism illustrated in Fig. 2 or the atypical features shown in Fig. 3. As in our previous work such areas of displacement were found to be of patchy distribution. In some parts of the methylcholanthrene hyperplastic epidermis none were encountered.

Fig. 8 is of a benign hyperplasia (19 days) from the edge of a healing wound centrifuged under the same conditions as the methylcholanthrene hyperplasia (Fig. 7). All the cells are of the spinous variety except the two in the lower left corner which are basal cells. The displacement of nuclear contents is quite noticeable, though it appears to be less than in Fig. 7 and there are no signs of centrifugal concentration of cytoplasm. But if in Fig. 8 an equally large proportion of the nuclei had been cut through their centers, as in Fig. 7, the displacement of nuclear contents might have looked about the same.

Examination of tissue outside the limited space shown in these illustrations, and of many other specimens, shows that in both methylcholanthrene and benign hyperplasia the nuclear contents of basal cells are more resistant to displacement by centrifugal force than those of spinous cells indicating a higher intranuclear viscosity as we have previously reported in our carcinogenic series. Certainly in both types of hyperplasia the intranuclear viscosity is lower than in normal (nonhyperplastic) epidermis of mice, in which, since there may be not more than two layers of cells, spinous cells as such are not differentiated. The point is that the decrease in intranuclear viscosity in the methylcholanthrene hyperplasia is progressive into squamous cell carcinoma; whereas that in benign regenerative hyperplasia is temporary and increases again when the epidermis returns to its previous condition.

Mineral constituents.—All the photomicrographs were taken with the same optical combination, distance, and exposure of tissues, prepared as nearly as possible in the same way. The finely divided, faintly bluish, white ash, said to be of Na and/or of K, is difficult to photograph and the illustrations are deficient as far as it is concerned.

A microincineration preparation of a 40-day methylcholanthrene hyperplasia, as seen in the dark field, is represented in Fig. 9. The heavy-looking white ash, consisting chiefly of Ca and Mg, is abundant in the basal cells, spinous cells immediately distal to them, and in the cells of the corneum, but is less in amount in the intervening spinous cells just beneath the corneum. In general it is more concentrated in the nuclei than in the cytoplasm except in the corneum.

When similar sections are stained with hematoxylin and eosin, or the Feulgen reaction for thymonucleic acid is applied to them, it is found that nuclei like those yielding this dense white ash are hyperchromatic as was reported by Horning and Richardson (14) in their study of cancer, and also by Scott and Horning (26).

A 50-day methylcholanthrene hyperplasia (Fig. 10) shows a further stage of mineral redistribution. Here the dense white ash of the cells forming epidermal projections into the dermis is conspicuous. The corneum is more mineralized than in Fig. 9 and the intervening band of spinous cells, with less mineral, is much wider.

A 70-day specimen appears in Fig. 11. While the amount of mineral is greater in the proximal and distal layers than in the intervening one, there are distinct regional differences in mineralization. It is fairly dense on the extreme right, then, passing to the left, is seen a vertical band of partly demineralized tissue. This is followed by a large epidermal peg which is rich in minerals and a wider vertical demineralized band. On the extreme left the mineralization is again considerable. It will be recalled that in rapidly growing embryonic skin, Scott (25) observed somewhat similar irregularities in the amounts of minerals.

A more extensive methylcholanthrene hyperplasia, though in a specimen treated only during a period of 60 days (as compared with 70 days), is pictured in Fig. 12. Here the demineralization is still more marked both proximally and distally. The outlines of the epidermal pegs can, however, be made out by the dense white ash, often of a single row of basal cells.

A contrast of the mineral constituents in two stages

DESCRIPTION OF FIGURES 5 TO 8

FIG. 5.—Benign hyperplasia of epidermis (19 days) in mouse of mixed stock. Note the organized type of cellular growth and uniformity in size of the cells in their respective layers. Compare with Fig. 3, particularly the spinous cells. Hematoxylin and eosin stain. Mag. × 1040.

FIG. 6.—Benign hyperplasia of epidermis (19 days) in mouse of mixed stock. There is marked intercellular and intracellular edema and prominence of intercellular bridges. Hematoxylin and eosin stain. Mag. × 1040.

FIG. 7.—Methylcholanthrene hyperplasia of epidermis (11 days) in New Buffalo mouse. Centrifuged specimen. Note the displacement of nucleoli and basophilic chromatin toward the centrifugal pole. Response is uniform throughout the spinous layer. Hematoxylin and eosin stain. Mag. × 1040.

FIG. 8.—Benign hyperplasia of epidermis (19 days) in mouse of mixed stock. Centrifuged specimen. Compare with Fig. 4. Note that the spinous nuclei with large nucleoli show displacement toward the centrifugal pole. The basal layer shows very little displacement. Hematoxylin and eosin stain. Mag. × 1040.

of benign regenerative hyperplasia is given in Figs. 13 and 14. Fig. 13 shows at the left the epidermis at the edge of a wound which has become hyperplastic (10 days). This dips down on the right into the wound where the epidermal sheet grown over the exposed dermis is thinner. The position of the basement membrane is not distinct in the photomicrograph. It is situated in the figure about 1.8 cm. below the surface on the right and extends toward the left roughly horizontally. Much of the white ash below it is of leucocytes. The hyperplastic epidermis represented is evidently somewhat demineralized but not so much so as the methylcholanthrene hyperplasia in Fig. 12. Supplementary stained sections seem to indicate that this demineralization is correlated with intense cellular activity. Fig. 14 illustrates a noticeably later stage in benign hyperplasia although the tissue was only taken one day after that used for Fig. 13; that is, 11 days subsequent to the making of the wound. The epidermis is from about 6 to 9 cells in thickness. It is heavily mineralized, especially the basal cells, proximal spinous cells, and corneum. That a reaccumulation of minerals has occurred is obvious. Moreover, the distribution of ash is fairly uniform. There is no lack of minerals in the upper spinous layer, as in Fig. 10, or in vertical bands, as in Fig. 11, both representing methylcholanthrene hyperplasias. MacCardle, Engman, and Engman (16) have reported a somewhat similar demineralization in the active lesions of neurodermatitis followed by a reaccumulation of minerals in healed lesions.

Discussion

By ordinary routine methods of fixation and staining we have found localized areas in the methylcholanthrene hyperplasias which differ markedly from anything observed in the benign hyperplasias. In them there is diversity of nuclear size (Fig. 1), hyperchromatism of both nuclei and cytoplasm (Fig. 2), and slight multinucleation (Fig. 3).

According to Guldberg (12) the appearance of the precancerous stages of tar cancer in mice "reminds one very much of the changes found in the epidermis of Bowen's precancerous dermatosis in man." Ewing (9) quotes Grutz as saying that "the histological picture of Bowen's disease is exactly reproduced by the later stages of epithelial overgrowth, occurring in animals receiving inunctions of tar products."

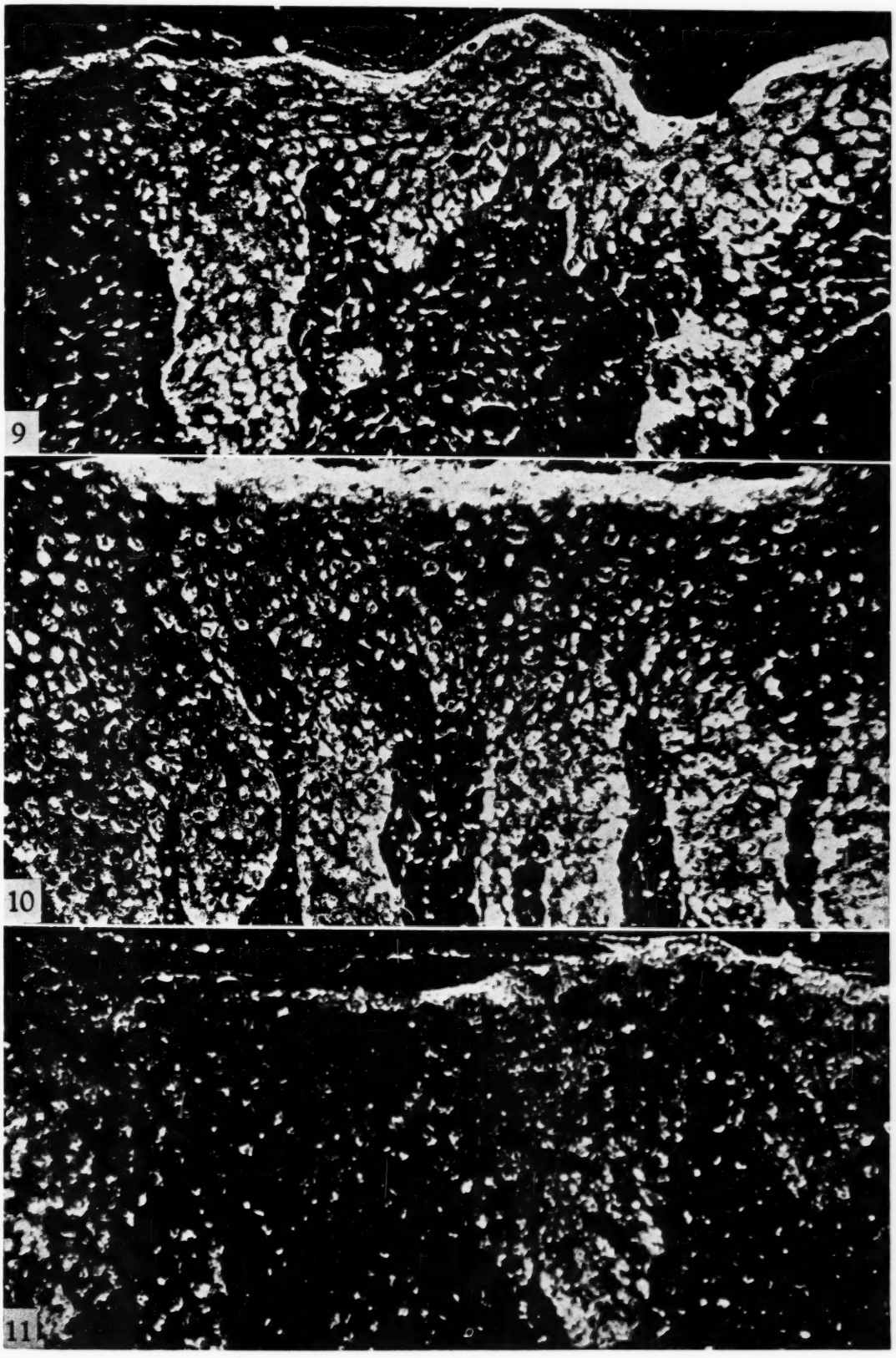
Comparison of our methylcholanthrene hyperplasias in mice with preparations from Bowen's disease in the Barnard Free Skin and Cancer Hospital collection reveals both similarities and differences. The "disorganization of the normal arrangement and size of the cells of the epidermis" mentioned by Montgomery (21) as one of the features of Bowen's disease, is present in our preparations but we are not sure of its absence in other sorts of hyperplasia. The "amitosis as well as the mitosis resulting in the formation of epithelial giant cells and giant epithelial cells," which he mentions, may occur to some extent in our specimens. It is possible that the cells possessed of two or more nuclei represented in Fig. 3 may have resulted from amitotic division of nuclei unaccompanied by division of cytoplasm. In a previous paper Cowdry and Paletta (6) described occasional gigantic epidermal cells, but these were in methylcholanthrene hyperplastic epidermises in which the neighboring cells departed but little from type and were unlike any giant cells illustrated by Montgomery though they resembled a cell possessed of a very large nucleus shown by Szodoray (28) in Bowen's disease. We do not regard them as an essential feature of the precancerous lesions. Mitosis is fairly common in our specimens. We have not, however, seen clumps of cells in mitosis immediately beneath the flattened cells of distal epidermal strata resembling those shown in Montgomery's Fig. 2a. There is some irregularity in keratinization, but we are doubtful as to how closely it approximates to the "individual cell keratinization" which he emphasizes. A few "corps ronds" may be seen though we have not observed in our specimens any significant number of cells with deeply stained nuclei and clear chromophobic cytoplasm, somewhat resembling Paget cells, and like those encountered in the Barnard Hospital's collection of Bowen's disease and illustrated in MacKee and Cipollaro's (17) Fig. 202 of Bowen's disease. Obviously, therefore, a more detailed comparison between our methylcholanthrene hyperplasias and Bowen's disease as well as the whole group of precancerous dermatoses

DESCRIPTION OF FIGURES 9 TO 11

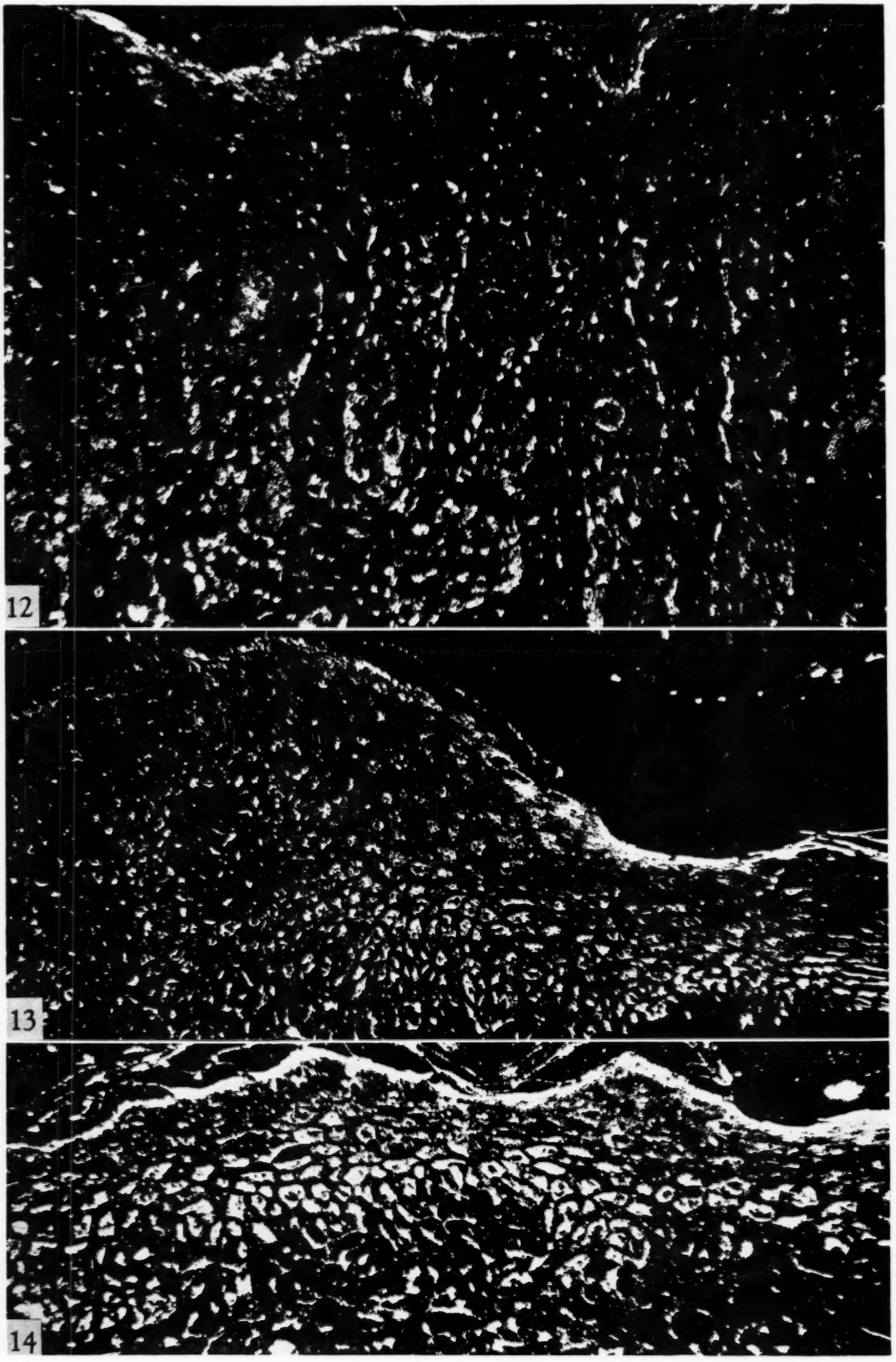
Fig. 9.—Methylcholanthrene hyperplasia of epidermis (40 days) in Swiss mouse. Microincinerated section. Observe the heavy deposits of white ash (Ca, Mg, Si) in the basal and spinous cells. The minerals are deposited mostly in the nucleus in the basal and suprabasal layer, except in the distal spinous cell layers and granular layers where much may be perinuclear. Mag. × 550.

Fig. 10. Methylcholanthrene hyperplasia of epidermis (50 days) in Swiss mouse. Microincinerated section. There are heavy deposits of calcium and magnesium in the cells of the hyperplastic downward projections. The keratin layer produced highly refractive white ash. Mag. × 550.

Fig. 11.—Methylcholanthrene hyperplasia of epidermis (70 days) in Swiss mouse. Microincinerated section. The irregularity of mineral residue is marked. Mag. × 550.



FIGS. 9 TO 11



FIGS. 12 TO 14

is necessary before reaching any conclusions as to the exact degree of similarity.

The areas described as showing diversity are probably foci in which the malignant transformation is likely to occur soon, if indeed it has not already taken place. We regard such lesions as probably "precancerous" arbitrarily restricting the term "cancer" to lesions in which there is evidence of invasion of the dermis. To recognize the latter is easy so that our demonstration of their presence in methylcholanthrene hyperplasia and of their absence in benign hyperplasia is of no practical value in determining the future of "precancerous" changes. It is necessary to find an earlier change which so conditions the epidermis as to make way for malignancy.

By ultracentrifugation we have tested intranuclear and to some extent cytoplasmic viscosities and have discovered that there is a decrease in intranuclear viscosity from the normal in both methylcholanthrene and benign hyperplasia. The photomicrographs (Figs. 7 and 8) show that this can occur in cells whose shape has not become atypical. The difference between methylcholanthrene and benign hyperplasias is that in the former this decrease in viscosity is progressive, as pointed out by Cowdry and Paletta (5), whereas in the latter it subsides. The much greater decrease in intranuclear viscosity of squamous cell carcinomas is characteristic, but unless it is more marked than that found in this and other types of benign hyperplasia it cannot be regarded as indicative of a precancerous condition. Moreover the technic is not such that it can be conveniently employed in the examination of a suspected lesion.

By microincineration we have noticed a regional variability in mineral constituents in methylcholanthrene hyperplasia (Fig. 11) not seen in benign hyperplasia. It is quite widespread and obtains in parts of the epidermis which do not exhibit focal areas of disorganization. Perhaps it is evidence of a basic instability, or lack of regulation, in mineral metabolism. Fortunately the method is not complicated so that it would not be a difficult task to compare the mineral skeletons of precancerous dermatoses with other dermatoses which seldom if ever become cancerous.

We hope to compare these methylcholanthrene and regenerative hyperplasias in mice by other microphysical and microchemical means. The essential preliminary is to separate the hyperplastic epidermis from the underlying corium so that the data collected will bear directly on it. We have found that this can easily be done by the cold dilute acetic acid method as detailed by Cowdry (3). For certain kinds of microanalysis the acid does not introduce experimental errors. When acetic acid is contraindicated the hyperplastic epidermis must be removed by other methods which will be described in a later paper.

Satenstein (23) has emphasized the point that in human epidermis only the cells that can proliferate are malignant or can become malignant. Keratinizing cells have lost this property. Consequently in mice, as in humans, a considerable fraction of the cellular population in methylcholanthrene hyperplastic epidermis is not precancerous. Since it is not feasible to dissect away or otherwise to remove this benign fraction, the microanalyses cannot be made to give data limited to the precancerous fraction unless the location of reactions can be determined microscopically.

Summary and Conclusions

Methylcholanthrene epidermal hyperplasia differs from regenerative benign hyperplasia in the following respects:

1. Regional diversity in structure is localized, irregular, and seemingly of haphazard distribution in methylcholanthrene hyperplasia; whereas, in benign hyperplasia it is definitely correlated with distance from the excised area. At the same distance in a given specimen, the structure is uniform in benign hyperplasia.

2. Focal variations in nuclear and cell size are of greater amplitude in methylcholanthrene hyperplasia than in benign hyperplasia, and nuclear hyperchromatism, as well as nucleolar size, is sometimes greater.

3. In methylcholanthrene hyperplasia the basement membrane appears to be more definite and exhibits a greater tendency to bulge into the dermis, there is more acanthosis and less affinity of the spinous cells for eosin, a more prominent granular layer, and slightly more hyperkeratosis than in benign hyperplasia.

4. Leucocytic infiltration and dilatation of spaces between the epidermal cells are both less in methylcholanthrene hyperplasia than in the immediate vicinity of the excised area in benign hyperplasia.

DESCRIPTION OF FIGURES 12 TO 14

Fig. 12.—Methylcholanthrene hyperplasia of epidermis (60 days) in Swiss mouse. Microincinerated section. Note extensive demineralization. Mag. × 550.

Fig. 13.—Benign hyperplasia of epidermis (10 days) in mouse of mixed stock. Microincinerated section. The extreme right is the edge of the active healing wound. Note the demineralization of the cells at the edge of the wound. Mag. × 550.

Fig. 14.—Benign hyperplasia of epidermis (11 days) in New Buffalo mouse. Microincinerated section. Note the reaccumulation of white ash (Ca, Mg, Si) in the basal and suprabasal cells of the hyperplastic epidermis when compared to an active healing wound of Fig. 13. Mag. × 550.

5. In both methylcholanthrene and benign hyperplasia the intranuclear viscosity, determined by displacement of basophilic chromatin and nucleoli under ultracentrifugal force, is less than in normal epidermis. The difference is that in the former the decrease continues to malignancy while in the latter it is only temporary.

6. In both there is a demineralization, particularly in the distal part of the spinous layer, but in methylcholanthrene hyperplasia there are local variations in mineral content not found in the benign hyperplasia.

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Chemical Configuration and Carcinogenesis*†

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For the past two years, we have been testing the carcinogenic activity of 70 compounds [1] of known chemical structure, closely related to benzanthracene, methylcholanthrene, dibenzanthracene, or benzpyrene. One of the objects of these tests has been to obtain further data on the limits of structural change within which a known carcinogen maintains its ability to induce tumors and the chemical nature of changes which will enhance, diminish, or destroy this faculty. The detailed results of these tests will be reported in later publications. The most striking general finding has been that slight changes in the structure or configuration of a compound are followed by major changes in carcinogenic activity.

A shift in position of one peripheral methyl group frequently transforms a potent compound into a completely inert form. For example, we have found in the benzpyrene group that the 9-methyl derivative produces tumors in 85 days, the 6-methyl in 160 days, almost twice as long, while the 2′- and 3′-methyl derivatives have so far produced no tumors at all. Again, while the 6-methyl derivative is fairly active, the 6-hydroxy has shown very slight activity.

The majority of simple changes in the structure of active compounds results in complete loss of carcinogenic activity. Among the 70 compounds we have tested, only 14 have proved active. In other words, the ability to induce tumors is confined, in the benzanthracene family, to a relatively small number of specific chemical substances and is not a general characteristic of the whole group.

Observations similar to these have often been reported, but it seems to us that too little emphasis has been laid on the inactive relatives of potent carcinogenic compounds. Inactive compounds may differ but little from their active isomers in physical properties, and their failure to induce tumors is a striking example of chemical specificity in carcinogenesis.

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[1] The compounds utilized in these experiments were selected and synthesized by Professor L. F. Fieser and associates of the Department of Chemistry, Harvard University.

In the light of such specificity in this group of carcinogenic agents, it is possible to assume, strictly as a working hypothesis, that the process of tumor induction depends upon a definite chemical reaction involving the carcinogen. Demonstration of a high degree of activity in biological derivatives of carcinogens would give some support to this hypothesis. A number of compounds have been prepared, principally by Dr. Hugh J. Creech (2-4) and Dr. John Wood (7), which might represent the product of interactions between hydrocarbons and substances present in tissues. These are chemical combinations between a carcinogenic nucleus and amines, proteins, and other organic radicals containing oxygen, sulfur, and nitrogen. A few of these have proved active but they are generally weaker than the parent compound.

Only one, 1,2,5,6-dibenzanthryl-9-isocyanate (Fig. 1), has produced tumors a little more rapidly than its parent compound, but it is improbable that this derivative could be formed from dibenzanthracene in the body.

A more direct approach to the chemistry of tumor induction is to study the actual metabolism of carcinogenic compounds after injection. A good deal of work has already been done on this problem and the evidence is fairly good that some of the hydrocarbons are excreted in the form of hydroxy derivatives (1). We have tested a number of such compounds, including 6-hydroxy-3,4-benzpyrene, 8-hydroxy-1,2-benzanthracene, 4′,8′-dihydroxy-1,2,5,6-dibenzanthracene, and 2-hydroxy-3,4-benzpyrene. All except the last compound have been under test for over 8 months. None has produced tumors except 6-hydroxy-3,4-benzpyrene and this has given only 2 tumors in a total of 40 mice.

It is quite possible, as Fieser (5) has suggested, that a "carcinogen is subject to two independent and competing reactions proceeding by different mechanisms, the one responsible for the induction of malignant growth and the other leading to detoxification." Extraordinary difficulties complicate the study of the local metabolism of carcinogens at the site of tumor induction. These compounds act in minute quantities, a small fraction of a milligram being sufficient to cause a tumor; and there is no ready method of chemical

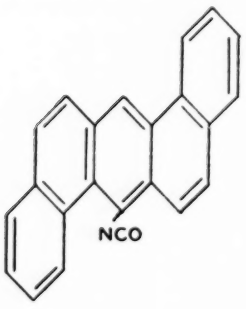
determination either for the injected compound or for its possible derivatives. Ultraviolet absorption spectra furnish a means of detecting and identifying minute traces of carcinogenic hydrocarbons, but metabolites can not be followed by this method after they lose the characteristic spectrum of the parent compound.

New Carcinogenic Compound

A new carcinogenic compound, 4,9-dimethyl-5,6-benzthiophanthrene (Fig. 2), may prove to be a useful tool in work of this sort. The compound was synthesized by Sandin and Fieser (6) and, in our preliminary experiments, has produced tumors in an average time of 116 days. This places it among the half dozen most active known carcinogenic agents and shows it to be of about the same potency as 9,10-dimethyl-1,2-benzanthracene (Fig. 2), its nearest relative in the benzanthracene series.

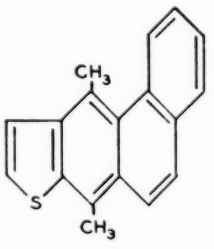
This compound is of special interest for several reasons. From the chemical point of view: (a) A new carcinogenic nucleus has been demonstrated which contains only 3 benzene rings. (b) Sulfur has been incorporated in the ring system. (c) The traditional benzanthracene nucleus has been shown nonessential for high potency compounds. From the experimental point of view, the presence of sulfur in the ring system would permit the substitution of radioactive sulfur, to serve as a tracer in following the metabolism of this substance during tumor induction.

1

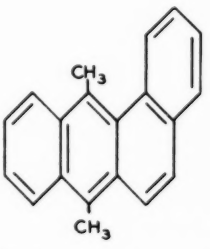


1,2,5,6 - DIBENZANTHRYL - 9-ISOCYANATE

2



4,9 - DIMETHYL - 5,6 - BENZTHIOPHANTHRENE



9,10 - DIMETHYL - 1,2 - BENZANTHRACENE

Figs. 1 and 2

Summary

Tests of the carcinogenic activity of 70 new compounds related to benzanthracene, dibenzanthracene, methylcholanthrene, and benzpyrene have given further evidence of a high degree of chemical specificity. Slight changes in structure are followed by major changes in activity. Several hydroxy derivatives of active compounds have shown little or no ability to induce tumors.

A new compound containing sulfur, 4,9-dimethyl-5,6-benzthiophanthrene, has proved highly carcinogenic. Radioactive sulfur in this compound could serve as a tracer for studying the local metabolism of an active carcinogen at the site of tumor induction.

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The Occurrence in Whole Blood of Material Influencing the Incidence of Mammary Carcinoma in Mice *

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In an effort to open up new leads and to further the study of a maternal influence affecting the incidence of tumors of the mammary gland in mice (3), an investigation of the possible role of the blood was started. Considerable progress has already been made in identifying a mammary tumor agent in the milk by Bittner (1), and subsequently by other workers. There are indications that the agent may be transmitted by the inoculation of spleen, thymus, and mammary tissue (2). This is a report of results of experiments with whole blood during the past year.

Materials and Methods

The recipient and control mice were of the second inbred generation following the nursing of inbred high-tumor JAX C3H mice on low-tumor inbred JAX C57 black mice. These fostered mice were obtained from Dr. J. J. Bittner. At weaning time a male and 4 litter-mate females were placed in each compartment of a mouse box. Breeding was allowed to proceed normally and the young of each litter were removed by the time they were 4 weeks of age. At 1 to 3 months of age 2 females of each group were injected subcutaneously with 0.5 cc. of whole blood diluted with an equal part of distilled water. Normal males and females of the inbred JAX C3H strain, 2 to 4 months of age, were used as donors. The donors were killed with massive doses of nembutal and the blood secured from the thoracic cavity, diluted with warm distilled water, and injected as quickly as possible. The blood of each animal was used individually and was not pooled. Following injection into subcutaneous tissue of the back, the blood was spread under the skin with slight pressure.

There were 99 mice in the control group and 109 in the experimental group at the time that the first tumor occurred. Animals dying before this time were not considered.

Results

The results are summarized in Table I. In the control group of 99 females, 6 tumors of the mammary gland have appeared at an average age of 248 days. Sixteen mice died tumor-free at an average age of 248.3 days. Seventy-seven are still living at about one year of age.

Table I: Summary of Results

Mice	Number of animals	Number of tumors	Per cent of tumors	Average age at appearance of tumor, days	Number dying tumor-free	Average age dying tumor-free
Experimental	109	20	19.16	267.3	15	256.3
Control	99	6	6.06	248.0	16	248.3
			13.10 ± 4.58	$D/\sigma = 2.68$		$P = 0.007$

In the experimental group of 109 females, 20 have had tumors of the mammary gland at an average age of 267.3 days. Fifteen mice died tumor-free at an average age of 256.3 days. Seventy-four are living and now are about one year of age.

All of the tumors were examined microscopically by Miss E. Fekete and were found to be adenocarcinomas.

An analysis of the difference between the experimental and control groups gives a value for P of 0.007, which indicates that the results at present might be obtained on a chance basis only once in 143 times.

Discussion

If it is accepted as significant that the animals received a mammary tumor influence through the injection of blood, it is evident that this was not sufficient

* This investigation was aided by grants from The Anna Fuller Fund and The Jane Coffin Childs Memorial Fund for Medical Research.

to raise the incidence of mammary carcinoma to the high level of tumor incidence occurring in the JAX C3H strain itself. Bittner, using fostered A strain mice, found that with the feeding of 0.9 cc. of milk 3 out of 7 developed mammary tumors by 16 months of age, but with 1.7 cc. of milk 8 out of 10 developed tumors by 16 months of age. If the blood contained the influence in a quantity approximately equal to that in the milk the 0.5 cc. of whole blood injected would be expected to affect less, rather than more, the return to a maximum high level of tumor incidence.

One important question raised but not answered is, if the mammary tumor inciter (MTI) is in the blood, why do the young not secure sufficient blood MTI during embryonic development to prevent the effectiveness of foster nursing? Is the placenta a screening mechanism or do the young not receive a sufficient quantity of the influence? The answer to these and other important questions must await further experimentation now in progress.

Summary and Conclusions

JAX C3H mice, which have had their tumor incidence lowered by foster nursing, were injected at 1 to 3 months of age with 0.5 cc. of whole blood from normal high-tumor JAX C3H male and female mice 2 to 4 months of age. Significant differences in tumor incidence now appear between the injected mice and their litter-mate controls. The mice of both groups are well beyond the average tumor age for breeding females of the untreated and unfostered JAX C3H strain.

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Experimental Studies on the Genetics of Spontaneous Leukemia in Mice*

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The genetic constitution of an individual largely governs its morphological development and its response to both internal and external stimuli. The inherited character may be expressed regardless of the nongenetic or environmental influences; or the nongenetic influences may completely suppress the genetic tendencies. Neither, in a large majority of the cases, is completely suppressed by the other. For a satisfactory study of one, it is desirable that the other be kept constant. But biological material is never constant and environmental changes are always present although they may not be readily determined. Changes in genetic constitution also occur universally and, while progeny may resemble their parents to all outward appearances, special breeding tests will show the existence of certain minor variations and such variations can be accentuated through suitable breeding procedures.

The extensive investigations herein reported were designed to evaluate the importance of genetic constitution in the development of spontaneous leukemia in mice.

Relatively little has been published concerning the genetics of spontaneous leukemia. The experiments dealing with the genetics of susceptibility to transmissible leukemia in mice have little, if any, direct bearing upon problems of inherited susceptibility to spontaneous leukemia. In transmission experiments, the ability of the host tissues to support the development of the transplanted leukemic cells is measured. Genetics of spontaneous leukemia concerns the constitutional factors which govern the development of leukemic cells.

Slye (11) was the first to present data concerning the heredity of leukemia in mice and suggested the inheritance of spontaneous leukemia as a simple Mendelian recessive character. Many of her data were obtained by analyses of past records and pedigrees; crucial breeding tests would have added much to the report.

Mercier (9) obtained evidence, later confirmed (10), that susceptibility to spontaneous lymphosarcoma was likewise inherited as a simple Mendelian recessive character. He recognized that environmental factors were involved, with approximately 50 per cent of the genetically susceptible individuals remaining free from lymphosarcoma. The absence of the disease among the F1 population and its appearance in the F2 generation in the expected ratio of 3:1 (but with only 50 per cent of the homozygous recessives showing leukemia) justified the conclusion that in these experiments leukemia in mice behaved as a simple recessive character.

The results of experiments of MacDowell and Richter (6) are at variance with the reports of Slye and Mercier. These authors used highly inbred strains of mice, one having an incidence of spontaneous leukemia of 1.3 per cent and the other 89.6 per cent. The incidence in the F1 generation was intermediate, with approximately 52 per cent developing leukemia (average of two reciprocal crosses). By backcrossing F1 mice to the low leukemia stock, the incidence was further reduced to about 33 per cent (average results from two reciprocal crosses). These authors demonstrated the presence of strong nonchromosomal factors contributed by dams of the high leukemia stock. Their main conclusion is that as the intrinsic factors for leukemia are decreased, the extrinsic factors play a relatively more important role in the prevention of the development of leukemia.

A recent paper by MacDowell, Potter, Taylor, and Ward (7) presents the results of a study of the segregation of "determiners" involved in spontaneous leukemia. Fifty male mice from the first backcross generation to the low leukemia stock were tested by crossing again to the low leukemia stock. The influence of extrinsic factors was minimized by the use of breeding procedures which permitted the rearing of all mice in one season of one year. Fifty backcross male families of about 50 mice each were studied. The incidence of leukemia in the families varied from 0 to more than 30 per cent. The "frequency distributions according to the incidence of leukemia present a symmetrical polygon with the mode in the 18 to 19 per cent class."

Plan of the Experiment

In the experiment here described, high and low leukemia stocks of mice were used which had been inbred by brother and sister or parent and progeny matings for more than 12 and 17 generations, respectively. The incidences of spontaneous leukemia (lymphoid and myeloid) in these stocks were approximately 70 and 2 per cent. The mice bred were used solely for the genetic studies. They were kept under as uniform environmental conditions as possible until natural death. Diagnoses were based upon gross examinations complemented by microscopic examinations whenever it seemed necessary. No attempt was made to obtain sections of tissues from all typical cases of leukemia nor were sections from negative cases examined for possible incipient stages of the disease. Certain matings in the two parental stocks

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were set aside as controls for the crossbreeding experiments and quotas for each of the 36 different types of matings were set at the beginning of the experiments. These were 240 mice for each F2 and F3 generation, 180 for each F1 and for both backcrosses of F2 mice to males of the parental stocks, and 120 for each remaining backcross generation. The average number desired in the 36 populations was 148 mice, mice dying from causes other than leukemia are considered arbitrarily as resistant to spontaneous leukemia. Should the investigator be able to control the many other diseases to which the mouse is susceptible, the accumulated data would lend themselves to much more accurate genetic analysis. In the present study, mice dying of causes other than leukemia before the 7th month were not tabulated because they could not

TABLE I: INCIDENCE OF LYMPHOID AND MYELOID LEUKEMIA IN AK AND RF MICE AND THEIR HYBRIDS *

Ak Susceptible P1 A/A	69.3% (212)	A/R	21.9% (192)	A/AR	24.8% [a] (117)	AxAR/A	46.7% [c] (30)
						AxAR/R	2.8% [d] (109)
				AR/A	28.8% [a] (104)	ARxA/A	50.0% [d] (90)
						ARxA/R	7.0% [d] (115)
				R/AR	2.6% [d] (117)	RxAR/A	4.7% [a] (107)
						RxAR/R	3.7% [a] (109)
				AR/R	2.8% [d] (108)	ARxR/A	8.6% [a] (116)
						ARxR/R	1.7% [a] (121)
				AR/AR	11.8% (228)	ARxAR/ARxAR	7.5% (213)
						ARxAR/A	14.5% [a] (159)
						ARxAR/R	4.1% [d] (170)
Rf Resistant P1 R/R	1.6% (188)	R/A	11.6% (173)	RA/RA	8.6% (222)	RAxRA/A	13.4% [a] (142)
						RAxRA/R	5.7% [a] (159)
						RAxRA/RAxRA	6.3% (285)
				RA/A	13.5% [a] (111)	RAxA/A	32.2% [d] (96)
						RAxA/R	4.3% [c] (116)
				A/RA	27.0% [d] (100)	AxRA/A	38.3% [a] (94)
						AxRA/R	10.1% [d] (79)
				RA/R	4.2% [b] (118)	RAxR/A	11.2% [b] (107)
						RAxR/R	0.0% [b] (76)
				R/RA	1.8% [d] (112)	RxRA/A	10.1% [d] (89)
						RxRA/R	3.9% [a] (103)

* The sign / separates immediate parents. Grandparents are not separated, while x is used to separate great-grandparents. The female is always on the left of each pair or sign.

† For backcross generations: a=no significant change; b=significant change, P=<0.05; c=significant change, P=<0.02; d=highly significant change, P=<0.01.

The figures in parenthesis indicate the number of mice studied.

while the actual number of mice which lived long enough to be included in the present summary and on which adequate diagnoses are available was 133 mice. The number of mice surviving in each hybrid generation to 7 months representing the progenies of many different matings are adequate for general conclusions.

An analysis of the genetic factors cannot be made without an arbitrary adjustment for some complicating factors. The arbitrary limits set may markedly affect the results and the conclusions. Probably one of the most important of these limits is the age after which accurately be classified as either resistant or susceptible to spontaneous leukemia.

Monocytic leukemia, which occurs spontaneously among a few mice of the low leukemia stock and their hybrids, has been eliminated from the general summary and is presented later in this paper as a separate entity.

RESULTS

A general tabulation of the data shows that under the conditions of these experiments susceptibility of mice to spontaneous leukemia is inherited probably as

a multiple-factor character. The results of all experiments are surveyed in Table I.

The incidence of leukemia in the F1 generation was intermediate to that occurring in the parental stocks. In the various backcross generations, the incidence of leukemia was always increased by matings to the high leukemia stock (significantly so in 6 of the 14 backcrosses), while matings to the low leukemia stock resulted in a lowering (significantly so in 10 of the 14 backcrosses) of the incidence of leukemia with two exceptions (Table I).

There is evidence in the F2 and F3 and certain backcross generations, however, that the incidence of leukemia is somewhat below, but not significantly so, that expected of a character dependent upon random segregation of multiple genetic factors. For example: the random mating of F2 mice should produce an F3 population in which the frequency of the various genotypes should be the same as that for the F2 population. Under uniform environmental conditions, therefore, the incidence of leukemia would be the same in the F2 and F3 generations. At least some of the observed difference can be attributed to the lower mean age at death for the F3 generations. These differences were 1 and 1½ months respectively for the two F3 populations. When mice of the same ages are compared on the basis of the per cent mortality from leukemia among those mice alive at the beginning of the month, it is obvious that the F2 populations not only have a somewhat higher total mortality from leukemia but that this difference was accumulating early in the life of the F2 populations as compared to their respective F3 populations. Intercurrent disease seemed to be responsible, at least in part, for this trend, as indicated by the following considerations.

Effect of environmental factors, mainly intercurrent disease.—The inclusion of F2, F3, and various backcross generations in the present study has made it inevitable that quotas for certain populations were completed before others. An attempt was made to organize the breeding program so that the colony would contain representative samples of the 36 various P1 and hybrid generations at all times during the course of the experiments. However, because of the nature of the work, the F1 populations preceded the F2 by about 2 months and the F3 by about 5 months (figured roughly, on the basis of mean time at birth plus one-half the average life span of the particular population). Thus, the environmental factors were not uniform upon the P1, F1, F2, and F3 generations. Pneumonia, one of the most important causes of death, has increased in the course of the experiments, as indicated in Table II.

Table II shows that in the F1, F2, and F3 generations there is a tendency for a reciprocal relationship between the incidence of leukemia and the incidence of pneumonia.

A relatively high incidence of pneumonia is expected among mice which are not destroyed by leukemia, but this assumption was not found to be true as regards the mortality figures of the P1 generations. Rf mice which had an incidence of spontaneous leukemia of less than 2 per cent lived to a relatively old age and only 12 per cent of them died of pneumonia, while in the high leukemia stock 69 per cent of the deaths are accounted for by leukemia and 22 per cent by pneumonia. Thus, the Ak stock was more susceptible to pneumonia than the Rf stock. It is quite possible that there is a genetic basis for susceptibility to pneumonia. There was a distinct tendency for a higher incidence of pneumonia among mice from backcross generations to the Ak stock as compared to the corresponding backcrosses to the Rf stock. Complementary genetic factors may have accounted for the greater incidence of pneumonia in the F1, F2, and F3 generations. However, it is probable that the increased incidence of pneumonia resulted from a greater exposure of the entire colony to its etiological agent. A larger number of experimental mice died of this disease in the later stages of the experiment before they had sufficient opportunity to develop leukemia than at the earlier stages of the experiment. Consequently, the incidence of leukemia in the later generations is probably less than would have been the case had pneumonia been adequately controlled.

TABLE II: INCIDENCE OF PNEUMONIA AND LEUKEMIA BY GENERATIONS

		P1 Per cent	F1 Per cent	F2 Per cent	F3 Per cent
Pneumonia	(Ak)	22	37	44	45
	(Rf)	12			
Leukemia	(Ak)	69	17	10	7
	(Rf)	2			

Maternal influence.—The observations of MacDowell and Richter indicated that a dam for the high leukemia stock exerted a greater influence than a sire upon the incidence of leukemia in the F1 hybrid generation. When the dam came from the high leukemia stock, the incidence of leukemia in the F1 generation was 61.9 per cent and in the reciprocal cross 42.5 per cent. Similar evidence was obtained by them by backcrossing F1 hybrids (C58/StoLi) to the low leukemia stock (StoLi) (Table III).

On the surface, our data agree with those of MacDowell and Richter with respect to the F1 generation (Table III) and show in the reciprocal crosses an incidence of leukemia of 21.9 and 11.6 per cent, respectively. This trend diminishes in the respective F2

and F3 populations (Table I) to the point where it is no longer significant. However, an analysis of the F1 data shows that the difference in the reciprocal crosses is due entirely to a marked difference in the incidence of leukemia among the males of the two F1 populations (Table III). It is probable that here we are dealing with some phenomenon other than that of maternal influence. Other possibiliities will be discussed later.

With respect to the backcross generations of F1 mice to the low leukemia stock (Table III, pairing No. 2), our data differ from those of MacDowell and Richter by not showing definite evidence of maternal influence, but this may be due to the low incidence of leukemia in this particular generation of mice.

Further information on maternal influence can be obtained by a study of three additional types of crosses (Table III, pairings Nos. 3, 4, 5) for which there are no analogies in studies published by others.

Table III: Influence of Maternal Factors on the Incidence of Leukemia

Mating		Pairing No.	MacDowell and Richter (6)		Cole and Furth			
			Mice, number	Leukemia, per cent	Mice, number	Leukemia, per cent		
						Total	In males	In females
F1	H/L *	1	139	61.9	192	21.9	28.1	15.6
	L/H	..	106	42.5	173	11.6	8.8	14.6
Backcross	HL/L	2	159	46.5	108	2.8	1.8	3.8
	L/HL	..	96	19.8	117	2.6	1.7	3.4
	HL/H	3	...	...	104	28.8	21.6	25.8
	H/HL	..	...	...	117	24.8	23.7	25.9
	LH/L	4	...	...	118	4.2	1.8	6.5
	L/LH	..	...	...	112	1.8	0.0	4.0
	LH/H	5	...	...	111	13.5	13.7	13.3
	H/LH	..	...	...	100	27.0	22.7	30.4

* H=high leukemia stock. (C58 or Ak.)
L=low leukemia stock. (StoLi or Rf.)

In pairing No. 3, a greater maternal influence may be expected on the part of the high leukemia stock dam than of the F1 dam since the former has a much higher incidence of leukemia than the latter, but the reverse effect was observed although the difference was not great. In the remaining three pairings of backcross generations, there is evidence for maternal influence but the figures obtained are significant only in the case of pairing No. 5 ($P = <0.02$). The relatively low incidence of leukemia in the progeny from LH/H matings in this pairing is not due to the earlier death of these hybrid mice, for they lived on the average longer than mice of any of the other three backcrosses.

Sex difference in incidence of leukemia.—Slye, and MacDowell and Richter interpreted their data as indicating that no difference exists between the sexes with regard to the incidence of leukemia in mice. Since our figures suggest a difference, the data of MacDowell and Richter, and Mercier were re-examined and are presented together in Table IV with figures from our experiments.

In the high leukemia stock of MacDowell and Richter there was only a slightly higher incidence among females than among males, but this stock may be regarded as so highly susceptible to the disease as to be unsuitable to demonstrate a sex difference. In both F1 generations of these investigators, however, females have a higher (not mathematially significant) incidence of leukemia than males. In the high leukemia stock of Mercier, the sex difference was very pronounced, females having an incidence of leukemia of 60.3 per cent and the males 38.2 per cent.

In 24 of the 36 different types of matings in our experiments, the incidence of leukemia was higher in the females, in 11 it was higher in the males, and there was no difference in one. Only occasionally was the observed difference significant and if all mice in the genetic experiments are grouped together there is still no significant sex difference. Some of these data are shown in Table IV. In addition, five lines of the high leukemia stock Ak (Table IV) were analyzed and in all, the females had a higher (significant for two lines) incidence of the disease than the males. When the X^2 values for each of the five lines of Ak stock are added (25.6) and Fisher's Table of X^2 entered at n equals 5, the sex difference is highly significant ($P = <.001$). These data in the pure lines of the Ak stock are significant and together with all other data presented in Table IV suggest that the female mouse is more susceptible to spontaneous leukemia than is the male.

This difference between sexes in the incidence of leukemia is not caused by an earlier death of the males because death from causes other than leukemia occurred on the average earlier among females than among males. It is noteworthy that leukemia occurs on the average earlier in the females than in the males.

Influence of pregnancies upon the incidence of leukemia.—It is well known that carcinomas of the mammary gland occur more frequently in bred than in virgin females. In order to study such a possibility with relation to leukemia, the data for the high leukemia stock Ak (9th and later generations) were analyzed:

	Females, number	Leukemia, per cent
Bred	103	72.8
Virgin	451	70.5

It is possible that a small number of the mice described here as virgins were bred. Nevertheless, the data can be interpreted to indicate that the incidence of leukemia among females is not influenced by pregnancy.

100 per cent by the various crosses, the incidence of spontaneous leukemia became progressively, but much more than proportionally, lower. This differs from the observations of MacDowell and Richter (6) who found a simple straight-line relationship, based on four points, between the per cent heredity from the high leukemia stock and the per cent leukemia. The more recent data (7) form a fifth point in this straight-line relationship at the level of 12.5 per cent heredity from the high leukemia stock. Dr. E. C. MacDowell, who very kindly spent considerable time and effort in studying our summarized data, suggested the plotting of the results in the form presented in Fig. 1.

In the data, there were 36 types of crosses which represented 9 different levels of per cents of Ak heredity. When the logarithm of the per cent leu-

TABLE IV: INFLUENCE OF SEX UPON THE INCIDENCE OF SPONTANEOUS LEUKEMIA

Investigator	Stock of mice	Sex difference ♀−♂, per cent	Females		Males	
			Mice, number	Leukemia, per cent	Mice, number	Leukemia, per cent
MacDowell and Richter	C58 (Leukemia)	1.3	336	90.2	270	88.9
	F1 C58/StoLi	12.4	66	68.2	73	56.1
	F1 StoLi/C58	4.6	42	45.2	64	40.6
Mercier	Lymphosarcoma	22.1	227	60.3	178	38.2
	F2	6.6	48	14.6	50	8.0
Cole and Furth	Rf *	0.7	103	1.9	85	1.2
	Ak * †	4.2	118	71.2	94	67.0
	F1 Ak/Rf	−12.5	96	15.6	96	28.1
	F1 Rf/Ak	5.8	82	14.6	91	8.8
	All 32 other genetic crosses	1.7	2,032	12.0	1,989	10.3
	Ak stock—line a	9.2	38	60.5	39	51.3
	Ak stock—line f	21.9	161	64.0	126	42.1
	Ak stock—line g	11.6	74	75.6	64	64.0
	Ak stock—line h	6.3	173	76.3	130	70.0
	Ak stock—line i	16.5	146	69.9	118	53.4

* Used as parental stock controls for the genetic experiments.
† These mice are also included in the totals for the lines f, g, h, and i of the Ak stock.

Mode of inheritance of susceptibility to spontaneous leukemia.—A complete genetic analysis of a character would involve the determination of the number and type of genes involved and their interactions with each other as well as with extrinsic factors. However, with most physiological characters it is not possible to explain satisfactorily all the data on the basis of 3:1, 9:7, or other simple ratios. Usually it is necessary, therefore, to assume that many genes are involved. The genetic analysis is still further complicated when extrinsic factors of many kinds and variable intensities modify the results either directly or indirectly.

It was not possible to analyze spontaneous leukemia as it occurs in our stocks of mice on a simple genetic basis. We were led, therefore, to assume that we were dealing with a multiple-factor character. In the genetic crosses, the Rf stock usually exerted more influence in lowering the incidence of leukemia than the Ak stock did in raising the incidence. In other words, as the total heredity from the Ak stock was reduced below

kemia is plotted against the per cent Ak heredity, it is obvious that a straight line results. The correlation is high ($r_{xy}=0.9083$) and the standard error of estimate is relatively low ($S.E_{y.x}=0.1827$). Expressed in a little different way, $(1-\sqrt{1-r^2xy})\times 100$, or 58.17 per cent of the observed relationship between the logarithm of the per cent leukemia and the per cent Ak heredity is associated with genetic factors. For one of the crosses at the 12.5 per cent level (RA × R/R) the incidence of leukemia was 0 per cent. Since the logarithm of 0 is infinity, it was not possible to plot the data for this cross in Fig. 1. The correlation is therefore based on 35 points.

Mean age at death does not enter directly into this correlation. As a matter of fact, as the per cent Ak heredity increases beyond 25 per cent, the mean age at death steadily decreases. It is therefore certain that differences in age at death in the various crosses has hindered, rather than enhanced, the straight-line

relationship of the logarithm of the per cent leukemia to the per cent Ak heredity.

Monocytic Leukemia

This type of leukemia has been described in the Rf stock (3). It has not been observed in any of the mice in this laboratory other than the Rf stock and their hybrid progeny and for this reason it has been separated from the myeloid and lymphoid leukemias and analyzed separately.

The diagnosis of monocytic leukemia [1] was based on microscopic examination of the blood-forming organs although in the course of this study we learned to recognize it at autopsy. Characteristic for this disease

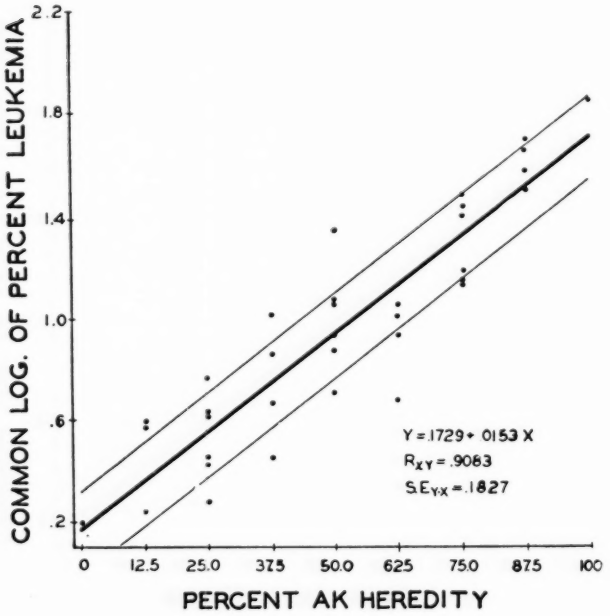

Fig. 1.—The relation between the percentage of heredity from the high leukemia stock, Ak, and the common logarithm of the per cent leukemia in the P1's and their various hybrid generations.

is a conspicuous enlargement of the liver, which is studded with minute grey, yellow-grey, or red areas. The lymph nodes as a rule are not enlarged but the spleen is enlarged to a variable extent. In both lymphoid and myeloid leukemias the liver may also be greatly enlarged but does not present the mottled appearance described, the lymph nodes are usually enlarged, and there is often a tumor mass in the mediastinum. Occasionally, however, there is with monocytic leukemia an isolated tumor-like enlargement of the mesenteric lymph nodes.

It has been possible to transmit monocytic leukemia and to show that the malignant monocytes (histiocytes) of the same strain may form either granuloma-like lesions or leukemic infiltrations (3). The spontaneous cases observed varied, some resembling the granulomatous, others the leukemic forms of this transmissible neoplasm.

In a small series comprising 76 mice of the Rf stock that received an intrasplenic injection of 1,2-benzpyrene, the incidence of monocytic leukemia was 9 per cent (4) as compared with 2.7 per cent monocytic leukemia occurring spontaneously. The gross and microscopic manifestations of this disease, however, were similar in both spontaneous and induced leukemias. Figs. 8-11 of this article (4) and Figs. 3, 12, 13, 17 of the preceding paper (3) may serve to illustrate the microscopic changes of monocytic leukemia occurring in the Rf stock. Figs. 1 and 2 of the latter paper (3) show the characteristic gross changes in liver and spleen.

Jørgensen (5) recognized the occurrence of lymphoid and myeloid leukemia in the Ak stock. He also observed the occurrence of an atypical form of leukemia in this stock which differs in our experience from the monocytic leukemias occurring in the Rf stock. Jørgensen concluded that only susceptibility to leukemia is inherited and not susceptibility to a particular type of the disease.

Monocytic leukemia occurs on the average at a much older age than the lymphoid and myeloid forms. It has, however, been observed as early as the 8th month. Of the 63 cases observed in the course of the genetic studies, 77 per cent occurred in mice 16 months of age or older. As with lymphoid and myeloid leukemia, there is a marked tendency for a higher incidence of monocytic leukemia among the females as compared to the males. Of the mice involved in the present study, 1.68 per cent of the females and 0.93 per cent of the males died of monocytic leukemia. In the Rf stock, the incidence of monocytic leukemia was 2.7 per cent. The frequency of monocytic leukemia in hybrid generations is shown in Table V.

The data in Table V suggest that monocytic leukemia is inherited as a dominant character. This is indicated by the high incidence of the disease in the F1 generation, as compared with the parental generations. In the hybrids it behaves as a multiple-factor character, the incidence approaching that in the Rf stock, but never reaching it. Intercurrent disease, particularly pneumonia, has probably influenced the incidence of monocytic leukemia in the later generations, as it influenced the myeloid and lymphoid types of the disease. Since monocytic leukemia occurs more frequently among older mice, it might be suspected that the incidence of the disease in the various generations is simply a function of the mean age at death. Although it is true that the progeny of backcrosses to the Ak stock are usually shorter lived than those of corresponding backcrosses to the Rf stock, primarily because of the effect of a high incidence of lymphoid and myeloid leukemia upon the mean age at death of the former group, there are some instances where

[1] The term is used in a broad sense and includes all neoplasms of monocytes with or without conspicuous blood invasion and with or without tumor formation.

differences in mean age at death cannot be used to explain the variations in the incidence of monocytic leukemia. Among the mice of the cross F1 × Rf stock/Ak the incidence of monocytic leukemia was 0.5 per cent and the mean age at death was 15.2 months. In the backcross to the Rf males, F1 × Rf stock/Rf, the figures were 1.5 per cent and 15.3 months. For the crosses F2/Ak and F2/Rf, the incidence of monocytic leukemia was 0.7 and 2.1 per cent and the mean age at death was 13.4 and 13.7 months, respectively.

There is no evidence in our data that would indicate that lymphoid and myeloid leukemia depend for their development upon different genetic factors, but no special attempt was made to study the inheritance of these two types of leukemia. It is evident, however, from the data presented that monocytic leukemia which occurs in the Rf stock and its hybrids is governed by some factors other than those which influence the development of lymphoid and myeloid leukemia.

difference is due to differences in the incidence of leukemia among the males. There is therefore no evidence for maternal influence unless it is expressed only in the male progeny and this seems very unlikely. The *nursing factor,* which is the important *maternal influence* in the development of carcinoma of the mammary gland, is not involved in spontaneous leukemia as shown by MacDowell and Richter (6), and by Barnes and Cole (1) who found that reciprocal fostering of mice of the high and low leukemia strains did not influence the incidence of leukemia among the fostered mice. The backcross generation of F1 mice to the low leukemia stock of MacDowell and Richter also suggested maternal influence. In the present study, no such trend was observed, possibly because of the relatively low incidence of leukemia in both backcross generations. Of the four possible reciprocal backcross generations, each involving approximately 200 mice, only one shows a significant difference.

TABLE V: THE INCIDENCE OF MONOCYTIC LEUKEMIA IN AK AND RF STOCKS AND THEIR HYBRIDS

Ak stock	0% (212)			Ak stock	0.8% † (432)	Ak ♂	0.3% † (310)
						Rf ♂	1.4% † (419)
		F1	2.4% * (365)	F2	1.8% * (450)	Ak ♂	0.7% * (301)
						F3	1.0% * (498)
						Rf ♂	2.1% * (329)
Rf stock	2.7% (188)			Rf stock	2.2% † (455)	Ak ♂	0.5% † (419)
						Rf ♂	1.5% † (409)

* Average results in the 2 possible crosses.
† Average results in the 4 possible crosses.
The figures in parenthesis indicate the number of mice studied.

DISCUSSION

Under the conditions of these experiments, the genetic constitution of the individual was a primary factor responsible for the occurrence of spontaneous leukemia. This is vividly demonstrated by the data in Table I, showing that by backcrossing females from the reciprocal F1 generations to Ak males the incidence of spontaneous leukemia was raised from 21.9 to 28.8 and 11.6 to 13.5 per cent. The second backcross to males of the leukemia stock further increased significantly the incidence to 50.0 and 32.2 per cent, respectively. This trend is still more significant when one considers that the general trend in the incidence of leukemia for the parental stock as well as the F2 and F3 generations was downward, primarily because of the increasing incidence of pneumonia facilitated by crowding of the animal room that occurred as the quotas were built up.

The phenomenon of *maternal influence,* which is particularly marked as regards carcinoma of the mammary gland, as shown by Bittner (2), was suggested for leukemia in mice by the data of MacDowell and Richter. It is also suggested, at least with respect to the F1 generation, by the present studies. However, further study of the F1 populations shows that the

The data were analyzed for *sex linkage* as suggested by the unexpected results in the reciprocal F1 crosses. Although the F1 results are easily explained on the basis of the sex linkage of genes for leukemia, further support for such a hypothesis is not found in the other data. No satisfactory explanation for the marked difference in incidence of leukemia between males of the reciprocal F1 crosses was found by a detailed study of the records on these mice.

The *sex difference* in incidence of spontaneous leukemia is supported by the data of MacDowell and Richter, Mercier, and a majority of the present data. It is not possible to check Slye's data, but she shows a few more cases among females than males in a species for which the sex ratio is in the neighborhood of 105 males to 100 females. At the present time, reasons for the sex difference in incidence of leukemia would be based entirely on speculation. Further experimentation is needed to locate the physiological basis for this difference. It is noteworthy that leukemia is almost twice as common in men as in women. Hormonal influence in the causation of lymphomatosis of chickens is indicated by the recent observations of Marine and Rosen (8) who assume that a hormonal imbalance with an excess of either male or female sex

hormones may have a stimulating effect upon lymphoid tissues.

The interesting relationship in which the logarithm of the per cent leukemia is a simple function of the per cent Ak heredity indicates that there is some order or rule to the relationship of heredity to spontaneous leukemia. It suggests a mode of action of the genes for leukemia which is somewhat kindred to the action of bacteria or possibly viruses in the causation of disease. Natural resistance to disease is usually a relative reaction, an excess of the etiological agent usually overriding the natural resistance. In experimental work with bacterial diseases it often takes ten times the dose of bacteria to produce twice the effect on the given population. Thus, it may be possible that the genes responsible for spontaneous leukemia are able to elicit the disease in a manner similar to the action of bacteria or viruses by overriding natural (genetic) resistance to a specific disease.

The incidence of spontaneous *monocytic leukemia* is relatively low. It behaves essentially as a dominant character with a very low degree of penetrance and is present in a stock which apparently is not genetically susceptible to spontaneous lymphoid and myeloid leukemia. Thus, in the stocks studied, different types of leukemia have a somewhat different genetic basis.

In the realm of *genetic resistance* to spontaneous neoplastic diseases, the evidence is overwhelmingly in support of the interpretation that the disease is a result of the interaction of both environmental and genetic factors. The genetic basis for resistance is apparently complex and cannot be explained in terms of simple dominance or recessiveness nor by a specific number of hereditary factors.

Data accumulated in recent years indicate that both intrinsic (genetic) and extrinsic (environmental) factors influence the occurrence of leukemia. It remains to determine the relative strength of intrinsic and extrinsic factors in the causation of this disease and the influence of one group of these factors upon the other. In similar problems involving domestic animals selective breeding can be practiced and it may be preferable to utilize the behavior of genetic tendencies in the control of the disease. Prevention of the human disease, however, depends upon a better knowledge of the extrinsic factors, particularly those which are capable of suppressing genetic tendencies.

Of the four sources of data concerning the heredity of leukemia in mice, two (Slye and Mercier) can be interpreted as indicating that the disease is inherited as a simple recessive character. The results obtained by MacDowell and Richter, and by us, can be best explained by assuming that spontaneous leukemia is inherited as a multiple-factor character and that environmental factors may modify genetic tendencies. The interpretations of the two groups of investigators are not incompatible with each other because the stocks of mice used by them were not the same and the observed differences can be explained by differences in the genetic constitution of the stocks studied.

The data described in this report and the observations of MacDowell and his associates are best interpreted by assuming that many genes are involved in the causation of spontaneous leukemia. The recent interesting studies of MacDowell and his associates support this conclusion. These investigators set up an experiment to test the genotype of males of the first backcross generation. This was accomplished by mating these males and females from the low leukemia stock and recording the incidence of leukemia among the progenies. In the F1 generation, theoretically all mice are genetically alike but in the backcross generation the number of different genotypes increases with the number of genes involved in the character studied. If one or two major genes were involved in susceptibility to spontaneous leukemia, then there would be only two or four different genotypes with respect to leukemia among the males from the first backcross generation. However, since the distribution of susceptibility among the 50 test families formed a normal curve, the data indicate that the males of the first backcross generation were of many genotypes and this is in agreement with the hypothesis that spontaneous mouse leukemia depends for its development upon many genetic factors.

Summary

A series of experiments was conducted for the purpose of determining the role of heredity in the development of spontaneous leukemia of mice. Two highly inbred strains of mice, one characterized by a high (70 per cent) incidence of lymphoid and myeloid leukemia, the other by a low (2 per cent) incidence of lymphoid and myeloid leukemia, were used from which F1, F2, F3, and various backcross generations were obtained for study. The experimental mice were kept under as uniform environmental conditions as possible and were observed until natural death. Diagnoses were based upon gross examination which was supplemented by microscopic studies when necessary. The genetic studies involved a total of 4,787 mice.

Analyses of the data show that the incidence of spontaneous leukemia is influenced by the genetic constitution of the mice and that many genes are probably involved.

Environmental factors, especially pneumonia, have influenced the frequency of leukemia.

No consistently significant evidence was found to support the hypothesis that nonchromosomal maternal

factors are involved in susceptibility to leukemia in mice.

A majority of our data, as well as that of other investigators, show that female mice tend to be more susceptible to spontaneous leukemia than males. Pregnancy was found not to affect the development of leukemia.

Monocytic leukemia which affects a small proportion (2.7 per cent) of the low leukemia stock, Rf, and their hybrids is also dependent upon the genetic constitution of the host for its development. It differs from the lymphoid and myeloid leukemia by being inherited essentially as a dominant character, and many genes are probably involved. In monocytic leukemia, environmental factors appear to be of major importance because in the inbred Rf stock the disease occurs with a very low degree of penetrance although all the mice are considered to be genetically alike. Thus, different types of leukemia may have different genetic bases. A comparison of our data with those of other investigators indicates that the same type of leukemia may be inherited in a different manner in different stocks of mice.

Conclusions

Susceptibility to spontaneous leukemia in hybrids of two experimental stocks studied is inherited, probably as a multiple-factor character, and is influenced by undetermined environmental factors. In the various crosses, the common logarithm of the per cent leukemia is a simple function of the per cent heredity from the high leukemia stock.

No consistent evidence was found that nonchromosomal maternal factors are involved in susceptibility to spontaneous mouse leukemia. Female mice have a higher incidence of leukemia than males.

The genetic basis for spontaneous leukemia may vary considerably with different stocks of mice.

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The participation of the senior author (R. K. C.) has been limited to the genetic analysis of the accumulated data.

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The Effect of Colchicine on the Mitotic Activity of the Brown-Pearce Rabbit Epithelioma

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The purpose of this paper is to clarify if possible the sequence of events in the mitotic activity of the Brown-Pearce rabbit epithelioma after single and multiple doses of colchicine. These data show that the response of this rabbit tumor to colchicine varies considerably with the individual tumor, indicating that biopsy must be done to determine the mitotic response at any designated time interval after the administration of colchicine.

Reviewing the literature on the effect of colchicine on tumors, both animal and human, one is struck by the disagreement in the data and opinion presented by the various authors (1, 4, 15). These papers, in general, agree that in tumors of mice and rats there are more mitotic figures in the metaphase visible in histological sections after colchicine than in sections from untreated tumor (1, 4, 7, 10-13, 15). Most of such data are based upon groups of animals that have received single injections of the drug. Some have used toxic and others subtoxic doses (6, 7). Many report *in vivo* experiments (1, 4, 7, 10-15); others report *in vitro* experiments (5, 14).

Materials and Method

Rapidly growing, 4- to 5-week-old, Brown-Pearce rabbit epithelioma in young, susceptible, New Zealand white rabbits was used throughout these experiments. Small biopsy specimens from the tumor mass in the testicle were taken under sterile precautions at empirical intervals of 5 to 7 hours, after the injection of colchicine [1] into a series of rabbits bearing tumors of the same age and source. Biopsy specimens (1 cu. cm.) taken from central and peripheral parts of the tumor, having a minimal amount of necrosis, were fixed in formaldehyde solution, U.S.P., diluted 1:10, and Zenker's solution, and stained in the usual manner with hematoxylin and eosin. A cover slip was lined and cut to fit the microscope eyepiece. The projected image of the lines made possible a uniform counting of the cells over a constant area. Approximately 3,000 cells were counted per biopsy section. The following are typical experiments.

Results

Experiment I.—Colchicine, dissolved in sterile saline, was injected subcutaneously into 17 rabbits, bearing 4-week-old Brown-Pearce rabbit epithelioma of uniform size (2.5 cm. x 4 cm.). Nine rabbits were given 0.25 mgm. per 100 gm. weight and 8 rabbits were given 0.125 mgm. per 100 gm. weight. Tumor material was removed at 5- to 7-hour intervals after one injection. Usually one testicle was removed from each of 2 rabbits at one interval, and the remaining testicle was removed at a subsequent interval. Representative specimens were taken from several areas for study; thus each rabbit supplied two testicles for study. The longest period before removing the testicle was 31 hours. Two rabbits receiving the larger dose died during the experiment. Another one with this large dose had a severe diarrhea.

Table I: Average Counts of Mitotic Figures from Data of Experiment I

Number of animals	Dose per 100 gm., in mgm.	Average count per 3,000 cells		
		5-7 hours	16½-18 hours	19-20 hours
3	0.25	194	..	..
4	0.25	...	93	..
4	0.125	183	..	..
4	0.125	...	..	75

The number of mitotic figures in the stained sections was counted. A maximum number of mitotic figures was obtained with both doses at the first interval of observation (Table I). There is no significant difference in the effect of the two doses used (0.125 to 0.25 mgm. per 100 gm. body weight). The number of mitotic figures fell progressively in the subsequent intervals (after 5 to 7 hours) except that there was an indication of a slight increase at 17 hours (Fig. 1).

Experiment II.—To determine whether the maximum effect is approximately at 6 hours and whether the secondary rise at 17 hours is constant, 7 rabbits were injected with a slightly smaller and safer dose

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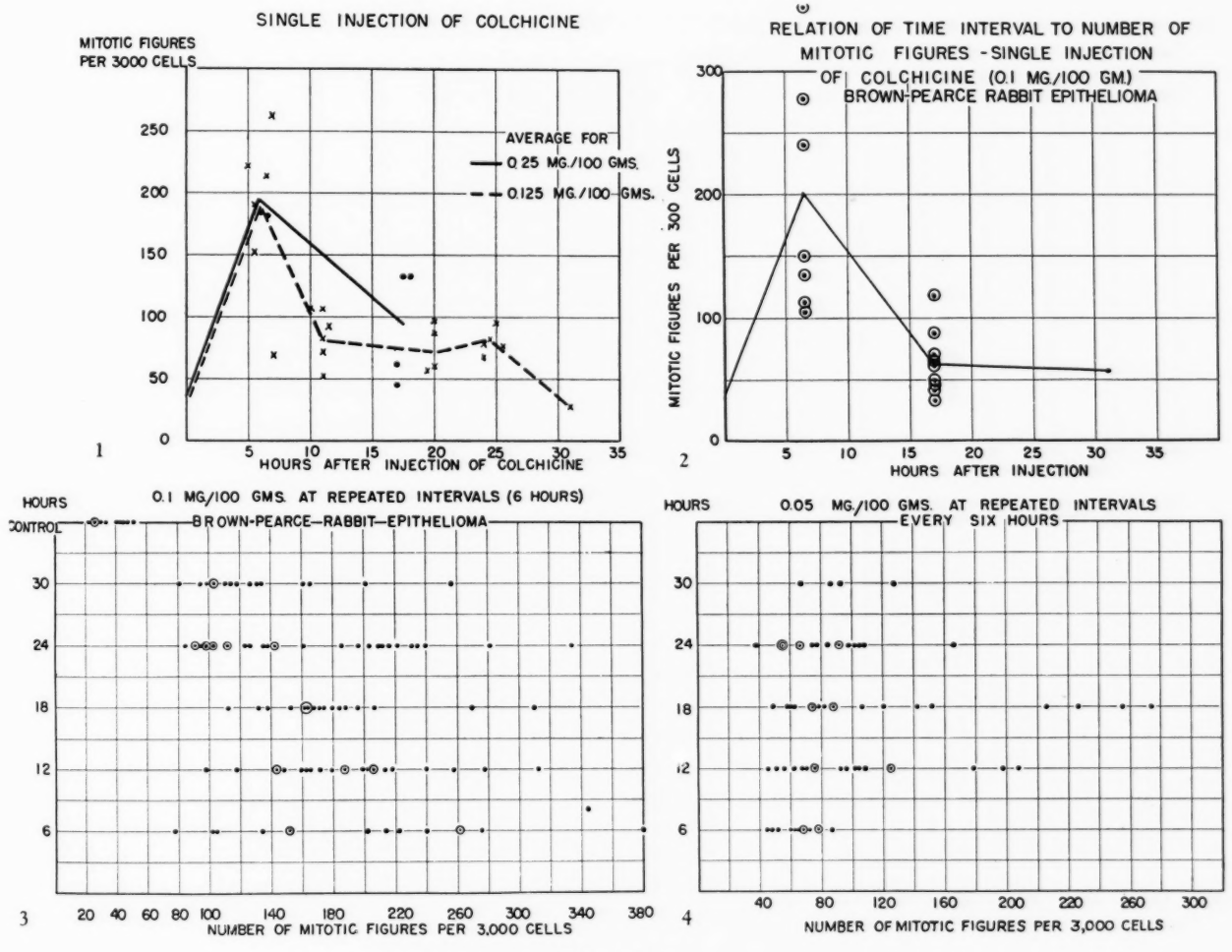
[1] The colchicine was supplied by the Abbott Laboratories.

(0.1 mgm. of colchicine per 100 gm. body weight). Specimens were taken from the testicles at 6, 17, and 31 hours. The maximum number of mitotic figures was observed at 6 hours, the other two intervals having less than one-third of this number. Fig. 2 shows the spread of the observations and the average effect graphically.

Experiment III.—The maximum effect of a single dose of colchicine in holding the tumor cell in the metaphase apparently occurs in the first interval (6 hours).

TABLE II: PERIOD OF EFFECT OF 0.1 MGM. OF COLCHICINE PER 100 GM. AT 6-HOUR INTERVALS FROM DATA OF EXPERIMENT III

Hours	Mean	Standard deviation	Number of observations	Standard deviation of mean	Significant
Control	37	10	10	3.1	...
6	162	72	24	14.7	Yes
12	198	44	22	9.1	Yes
18	179	47	19	4.3	No
24	135	64	24	12.8	Yes
30	132	44	16	11.0	No



FIGS. 1 TO 4

Equal doses of 0.1 mgm. of colchicine at 6-hour intervals were given to study the cumulative effect. The maximum cumulative effect was produced by the second injection at 12 hours. Although there is considerable spread, the average figure at 6 hours is significantly different from and less than the average figure at 12 hours. The 18-hour average figure as compared to the 12-hour average figure is not significantly different when calculated and thus does not show an increase in mitotic activity. There is a significant fall after 18 hours (Table II; Fig. 3).

The distribution of mitotic figures in the sections taken at the same interval appears in Fig. 3. At 6 hours, the extremes range from 78 mitotic cells per 3,000 cells to 380 mitotic cells per 3,000 cells.

Experiment IV.—A further reduction in dosage to 0.05 mgm. of colchicine in repeated equal doses (in 6 hours) results in approximately half the number of mitotic figures obtained with the 0.1 mgm. dosage (Fig. 4). The maximum cumulative effect occurs during the 12th to 18th hour periods (Table III).

The cumulative effects with 0.1 and 0.05 mgm. of colchicine are roughly parallel (Fig. 5) although the number of mitotic figures is reduced to about 50 per

cent with the lower dose, for if the values obtained with the lower dose are multiplied by a factor of two, the spread and average almost superimpose those obtained with the higher dosage. Using a larger, single dose (above 0.1 mgm. in the previous experiments) did not show a significant increase in the number of mitotic figures (Table I). Thus 0.1 mgm. is apparently optimal for a single dose and apparently produces an optimal effect in repeated doses, judging from our limited data.

Experiment V.—Atropine has been considered antagonistic to colchicine (8). Three rabbits were given two doses of colchicine (0.1 mgm.) and atropine (0.4 mgm.) combined, with a 6-hour interval between the

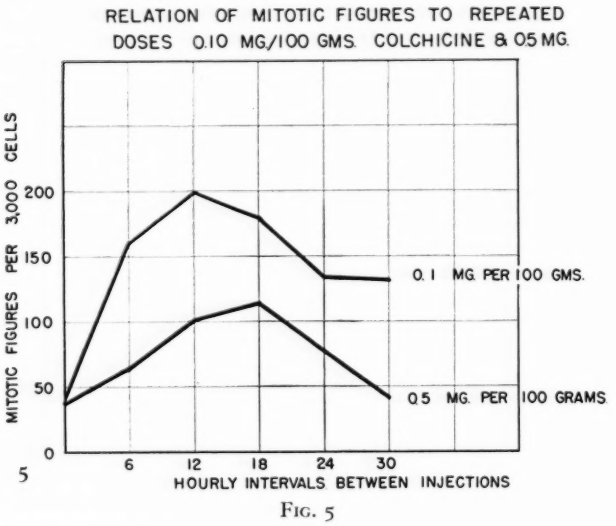


FIG. 5

doses. Table IV shows the counts of the mitotic figures obtained. The atropine did not change the effect of the colchicine in the dose used during the 6-hour observation, which is the period of maximum mitotic figure count. Since all of the values are within the spread of the other data, the experiment was not carried further.

DISCUSSION

The rabbit is quite resistant to colchicine. When colchicine is administered to a rabbit with an actively growing Brown-Pearce rabbit epithelioma, the cells in the metaphase stage of mitotic division are seen to be increased in number over the controls. The magnitude of this effect varies with the individual tumor. Tumors of the same age and from the same generation but in different sites, even in the same animal, do not give consistent results when treated with the same dosage of colchicine.

Colchicine administered in various doses shows considerable variation in its effect upon mitosis, roughly comparable to the dosage employed. The mean value obtained from single doses after 6 hours for 8 samples given more than 0.125 mgm. per 100 gm. is 188; that for 24 samples given 0.1 mgm. per 100 gm. being 162; and that for 12 samples given 0.05 mgm. per 100 gm. being 65.

The maximum number of mitotic figures in other animals was observed by other workers to have occurred at various periods extending over a range from 6 to 24 hours, and the increase varied from 12 to 38.2 per cent in the colchicinized animals (5, 9-12).

In our experiments with the Brown-Pearce rabbit epithelioma, repeated doses of 0.1 mgm. or 0.05 mgm.

TABLE III: PERIOD OF EFFECT OF 0.05 MGM. OF COLCHICINE PER 100 GM. AT 6-HOUR INTERVALS FROM DATA OF EXPERIMENT IV

Hours	Mean	Standard deviation	Number of observation samples	Standard deviation of mean	Significant
Control	37	10	10	3.1	...
6	65	13	12	4.7	Yes
12	102	47.5	18	11.4	Yes
18	117	61	20	13.9	No
24	78	25	12	7.3	Yes
30	42	40	4	20.0	...

TABLE IV: ANTAGONISTIC ACTION OF ATROPINE AND COLCHICINE FROM DATA OF EXPERIMENT V

Hours	Average count Rabbit I	II	III	Control 0.1 mgm.	Spread
6	60	121	200	162	78-380
12	107	Necrosis	Necrosis	198	98-312

TABLE V: MITOTIC INDICES

Hours	0.1 mgm.	Mitotic index	Hours	0.05 mgm.	Mitotic index
6	162	4.5	6	65	1.8
12	198	5.5	12	102	3.0
18	179	4.9	18	117	2.8
24	135	3.7	24	78	2.1

cause the number of mitotic figures to increase up to 12 to 18 hours. The number of figures in the tumor section after this interval falls slowly. The actual counts for the smaller dosages (Fig. 4) are less although the curves are roughly parallel.

Even though it can be predicted that a group of these rabbit tumors will show an increase in the number of mitotic figures after the injection of colchicine, in the individual tumor, repeated biopsies must be performed to determine whether a response of sufficient magnitude has been obtained. This is essential if we postulate that irradiation is most effective during the mitotic phases and attempt to use colchicine to bring the tumor into the most sensitive and therefore favorable state for destruction by irradiation. Obviously, our results indicate that such a state is not achieved by colchicine for this tumor since in no case has the ratio of the mitotic

figures in the treated (150 in 3,000 cells) to the controls (37 to 3,000 cells) reached beyond 5.5 at the maximum (Table V). Obviously irradiation must destroy tumor cells which are not morphologically in the metaphase or other phases of obvious mitotic activity. This tumor is considered to be highly malignant yet normally only about 1 per cent of its cells are in a stage of mitotic activity. Colchicine elevates this number to individual maximum high values of 12 per cent. Since we have been unable to obtain a definite minimal lethal dose of roentgen radiation *in vivo* for this tumor,[2] these data do not give sufficient encouragement for us to undertake the prolonged and extensive controlled experiment necessary for the study of the combined effects of colchicine and roentgen radiation at this time. Considering all of these features and the high toxicity and its unpredictable effects on the individual, we are led to suspect that colchicine is of little value as an additional aid to radiation therapy of this tumor.

Conclusions

1. Colchicine definitely causes an increase in the mitotic figure (metaphase) count in the Brown-Pearce rabbit epithelioma.

2. The optimal dose is 0.1 mgm. per 100 gm. body weight, and produces the maximum effect in single doses in approximately 6 hours after injection. The effect then gradually wears off.

3. With repetition of the dose at 6-hour intervals, the maximum effect occurs at 12 hours and declines thereafter. The average number of mitotic figures obtained with repetition of 0.1 mgm. per 100 gm. body weight was approximately twice that with 0.5 mgm. This numerical relationship was not obtained with single doses.

4. Although the average response in a group can be predicted for a given dosage, the response of the individual tumor varies greatly so that biopsy must be resorted to in order to determine the magnitude of its response to the drug.

5. The results were so unpredictable that a trial of the effect of colchicine and roentgen radiation did not seem feasible at this time.

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[2] Unpublished work with S. Larson indicates that this is somewhere above 18,000 r single massive dose.

Steroid Excretion in Cancerous and Noncancerous Persons

II. Urinary Estrogens*

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In a previous paper (9) data were presented on the estrogenic titer of the "estrone," or weak phenolic fraction, and the "estriol," or strong phenolic fraction, of the urine from certain cancerous women before and after the injection of estrone and a combination of estrone and progesterone. In those experiments, the method of estrogen assay employed was a modification of the Astwood (1) technic. It seemed worthwhile to use a more conventional technic for the assay of estrogen. The patients previously studied were a selected group of women having carcinoma of the cervix and fundus. We were interested to see if these findings could be extended to cancerous persons generally, particularly because Ross and Dorfman (12) have since reported no unusual total urinary estrogen in the cases of 4 women with cancer of the breast.

Subjects and Methods

The urines from eight sets of subjects were collected in 48- to 72-hour lots, with toluene as the preservative. The cancer cases were patients at the Worcester City Hospital and consisted of men and women in early to middle stages of the disease. Urines from cachectic, moribund, and post-operative cases were not collected. All diagnoses were confirmed by either biopsy or autopsy. The age distribution of the patients and types of disease are given in Table I. The control groups consisted, except as noted in Table I, of noncancerous patients in roughly the same physical condition as the cancerous patients. No individual patient contributed more than 6 per cent of the total (except in the series II noncancerous males of Table I). As can be seen from Table I, miscellaneous cases contributed to the urine pools. This was desired in order to discover if any striking alteration of estrogen excretion characterizes cancerous persons generally. Patients with tumors of the adrenal cortex were not included.

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The method of hydrolysis and extraction employed has been previously described (10). The alkaline phenolic fractions obtained were neutralized, extracted with ether, and brought to dryness. The dried extracts from individual urines were pooled by redissolving in ether and the pooled sample was washed twice with a saturated solution of $NaHCO_3$ followed by two wash-

Table I: Sources of Urines Contributed to Urine Pools

Urine pool	No. liters	Types of contributors	Age range in years
Noncancerous ♀ I	124	¾ from nonhospitalized normal women; ¼ from cases of ovarian cyst, nonmalignant cervical erosion, neurosis	18 to 63
Noncancerous ♀ II	152	All from 10 advanced cases of pulmonary tuberculosis confined to bed	4 to 60
Cancerous ♀ I	208	Malignancies of uterus and cervix (36%), ear and antrum (21%), stomach and intestines (18%), breast (16%), lung (7%), spine (2%)	32 to 80
Cancerous ♀ II	121	Malignancies of cervix (62%), breast (17%), stomach and intestines (13%), and spine (8%)	32 to 79
Noncancerous ♂ I	210	All from nonhospitalized normal men	26 to 55
Noncancerous ♂ II	166	9/10 from nonhospitalized normal men; 1/10 from cases with arteriosclerotic heart disease and acute orchitis	16 to 60
Cancerous ♂ I	441	Malignancies of stomach and intestines (31%), bladder (31%), penis (18%), prostate (12%), lung (3%), throat (2%), brain (2%), pancreas (1%)	29 to 81
Cancerous ♂ II	191	Malignancies of mouth (30%), bladder (29%), bone (19%), prostate (14%), brain (6%), rectum (2%)	40 to 83

ings with distilled water. Ketonic material was removed by the use of the Girard reagent (7). The remaining nonketonic fraction was separated into weak phenolic and strong phenolic fractions by the method of Cohen and Marrian (3). Urinary estrone should be contained in the ketonic fraction since estrone is the only ketonic estrogen that has been isolated from human urines. Estradiol is the probable estrogen in the nonketonic weak phenolic fraction (10) and estriol in the nonketonic strong phenolic fraction (3).

All assays were conducted on spayed female rats. Our routine procedure involves injection of estrogen in 3 subcutaneous injections, 4 hours apart, once every 5 days. Only those animals showing positive vaginal smears at 48 hours after the first injection are employed for assay purposes at the succeeding injection period. Negative animals are primed by the injection of a total of 1.5 γ estrone in the 3 injections. Animals which show negative smears after two primings are discarded. By this method with our strain of animals 1 rat unit (50 per cent positive) is equal to 1 μgm. of estrone, 1 μgm. of estriol, and 0.12 μgm. of estradiol. In practice we employ a minimum of 16 animals for an assay and attempt to approximate the 50 per cent point. All materials are dissolved in olive oil. Standard curves for estrone, estriol, and estradiol in olive oil were constructed using recrystallized materials of constant melting point. In the second set of four types of subject, aliquots of each fraction were assayed; in the first set no assay was made of the total phenolic material but of every separation thereafter (Table II). Results are expressed in estrogenic activity per liter.

Table II: The Estrogenic Titer of Various Phenolic Fractions of Pooled Urine Samples *

Type of subjects	Series	1. Total phenolic r.u. per liter	2. Ketonic phenolic (estrone) r.u. per liter	3. Nonketonic phenolic r.u. per liter	4. Nonketonic weak phenolic (estradiol) r.u. per liter	5. Nonketonic strong phenolic (estriol) r.u. per liter	6. Sum of assays of 2, 4, and 5 r.u. per liter
Noncancerous ♀	I	.....	1.13 ± 0.11	2.56 ± 0.31	2.98 ± 0.33	0.83 ± 0.10	4.94
Cancerous ♀	I	.....	0.19 ± 0.02	2.85 ± 0.23	0.75 ± 0.09	0.35 ± 0.04	1.29
Noncancerous ♀	II	2.35 ± 0.29	0.21 ± 0.02	1.15 ± 0.13	0.57 ± 0.05	0.68 ± 0.08	1.46
Cancerous ♀	II	2.06 ± 0.20	0.16 ± 0.01	1.30 ± 0.14	0.30 ± 0.03	0.28 ± 0.03	0.74
Noncancerous ♂	I	.....	0.39 ± 0.04	1.93 ± 0.23	0.17 ± 0.02	0.28 ± 0.03	0.84
Cancerous ♂	I	.....	0.33 ± 0.02	2.22 ± 0.26	0.74 ± 0.08	0.42 ± 0.05	1.49
Noncancerous ♂	II	2.16 ± 0.26	0.35 ± 0.04	1.26 ± 0.13	0.48 ± 0.04	0.16 ± 0.02	0.99
Cancerous ♂	II	1.71 ± 0.19	0.32 ± 0.04	2.18 ± 0.26	1.09 ± 0.11	0.28 ± 0.03	1.69

* The standard errors for each value given are calculated from the formula $S.E. = \pm\sqrt{\frac{p \cdot q}{n}}$ where p = the per cent positive smears, q the per cent negative smears, and n the number of animals.

Results

The data on the various groups of subjects are summarized in Table II.

An inspection of these data clearly reveals the following differences: (a) the sum of the rat units of the three final fractions is higher in the noncancerous women than in the cancerous women; this is reversed in the case of the men's urines (Table II, column 6); (b) the strong phenolic nonketonic fractions show uniformly more activity in the noncancerous women's urines (Table II, column 5); (c) the weak phenolic nonketonic fractions of the cancerous men's urines are uniformly of higher titer than the same fractions from the urines of noncancerous men (Table II, column 4). Within the individual series other differences appear. Thus in series I the ketonic fraction of the urines of noncancerous women has about 6 times the activity of the same fraction from the urines of cancerous women (Table II, column 2). This large difference is markedly reduced in series II in which comparison is made between urines from tuberculous and cancerous women. Again, the titers of the nonketonic phenolic fractions of the women's urines do not differ significantly in the two series (Table II, column 3). But when these are separated into weak and strong phenolic fractions a higher titer is obtained for the extracts from noncancerous urines. Among the males' urines there is no significant difference between the titers of the ketonic fractions (Table II, column 2), the titers of the nonketonic fractions tend to be higher in the cancerous men (Table II, column 3), and further separation shows this difference even more strongly.

In Table III is a comparison between the titers of the total nonketonic material and the sum of the titers of weak phenolic and strong phenolic nonketonic fractions. These data indicate that the fractionation of the nonketonic extracts leads to an increase (Table III, series I) or no significant change (Table III, series II) in the estrogenic titers of noncancerous women, whereas the same extracts of cancerous women's urines show a decrease in titer. A similar decrease occurs on the fractionation of extracts of men's urines. This decrease appears to be restored on recombining the weak and strong phenolic fractions in their original proportions (Table III, noncancerous men, column 1). This implies that the men and the

noncancerous women excrete nonketonic materials which enhance the activity of certain urinary estrogens, and that these materials are fractionated by the Cohen and Marrian procedure; the noncancerous women, on the other hand, excrete no such substances, their urines containing, if anything, inhibitors of estrogenic activity. We have assayed various combinations of pure estradiol and estriol and find neither enhancement nor inhibition of activity.

TABLE III: A COMPARISON OF THE ESTROGENIC TITERS OF THE NONKETONIC EXTRACTS BEFORE AND AFTER SEPARATION INTO WEAK AND STRONG PHENOLIC FRACTIONS

Type of subjects	Series	1. Nonketonic phenolic r.u./liter	2. Nonketonic weak phenolic plus nonketonic strong phenolic r.u./liter	3. 2 as per cent of 1
Noncancerous ♀	I	2.56	3.81	149
Cancerous ♀	I	2.85	1.10	39
Noncancerous ♀	II	1.15	1.25	109
Cancerous ♀	II	1.30	0.58	45
Noncancerous ♂	I	1.93 (1.99)*	0.45	23
Cancerous ♂	I	2.22	1.16	48
Noncancerous ♂	II	1.26	0.64	51
Cancerous ♂	II	2.18	1.37	63

* The figure in parenthesis is the titer of the nonketonic fractions (weak and strong) upon recombination in the original proportions.

reverse occurs with the weak phenolic extracts. The 40:1 ratio reported for pure estriol is not obtained, being about 5:1 in one instance and 13:1 in another (Table IV, column 4). There is no evidence in these partitions for the further removal of enhancing material, in fact the data on the strong phenolic fractions suggest that inhibitory material is removed particularly from the extracts of the urines of cancerous men. The higher titer of the strong phenolic fraction of cancerous men previously noted thus becomes even more marked. The recoveries from the weak phenolic fractions are nearly quantitative, since there is no statistically significant difference between the titers of the unfractionated material and the sum of the titers of the two fractions.

DISCUSSION

The data of this paper are presented as indicative merely of possible modes of estrogen metabolism in cancerous persons generally. The differences in estrogen excretion noted may not be due to the presence of malignancies in the cancer subjects. We note first of all that most of our control groups contain on the average somewhat younger persons and a larger proportion of "healthy" individuals. Among the women a somewhat higher proportion of postmenopausal ages is included in the cancerous group. This would imply that we must ascribe to differences in age and physical condition the three clear-cut differences noted; *i.e.,* decrease in the sums of the titers of the three principal fractions in cancerous women and an increase in cancerous men, higher "estriol" titers in noncancerous women's urines, and higher "estradiol" titers in cancerous men's urines. We can understand this in the case of the women wherein a decrease of estrogen excretion with illness and age is implied, but the opposite implication in the men is striking.

We should note, too, that the differences observed may be ascribable either to "normal" variations in estrogen excretion or variations in the assays themselves. The latter we may discount since our standard data have been repeatedly checked without finding sig-

TABLE IV: THE PARTITIONING OF THE ESTROGENIC ACTIVITY OF CERTAIN NONKETONIC URINE FRACTIONS BETWEEN BENZENE AND 0.3 M Na_2CO_3

Type of subjects	Series	Fraction partitioned	1. Titer before partitioning r.u./liter	2. Na_2CO_3 fraction r.u./liter	3. Benzene fraction r.u./liter	4. Per cent of activity in Na_2CO_3 fraction 2 as per cent of 2 and 3
Noncancerous ♂	I	Strong phenolic	0.28	0.35	...	..
Cancerous ♂	I	Strong phenolic	0.42	0.60	0.12	83
Cancerous ♂	II	Strong phenolic	0.28	0.83	0.06	93
Cancerous ♂	I	Weak phenolic	0.74	0.20	0.74	21
Noncancerous ♀	I	Weak phenolic	2.98	0.21	2.45	8

This evidence for the presence of inhibitory and enhancing materials led us to attempt a further purification of certain of these urine fractions. We observed that the strong phenolic nonketonic extracts contained large amounts of tarry materials having a cresol-like odor. It has recently been reported (15) that estriol, the presumably native estrogen of these fractions, may be extracted from benzene solution by 0.3 M Na_2CO_3. By this method 40 parts of estriol are partitioned into the Na_2CO_3 solution to 1 part in the benzene. We have applied this partitioning to three strong phenolic and two weak phenolic nonketonic fractions. The result was a notable segregation of most of the tarry material into the benzene fraction. The data on estrogenic activity (Table II) accords roughly with expectation; *i.e.,* most of the activity of the strong phenolic extracts is found in the Na_2CO_3 fraction whereas the

nificant departures from expectation. The former we think is well covered by the quantities of starting material employed, the smallest urine pool (121 liters in series II, cancerous females) represents roughly 100 days' excretion of a single individual. The titers in series I and series II are, all things considered, in quite good accord. The exception is in series II where the various fractions of women's urines have lower titers than in series I, especially in the control group of tuberculous women. These latter were chosen as contributors purposely in order to obtain specimens from "very sick" persons. They were all confined to bed in very advanced stages of pulmonary tuberculosis. Even these women show the characteristic differences noted.

Finally, the peculiarities of these data, as those on all pooled urines, may be due to the inclusion in the urine pools of certain pathological individuals whose markedly abnormal estrogen excretion might change the general picture. The consistency in the outstanding differences from series to series would militate against this.

It is clear that if the observed peculiarities in estrogen excretion are ascribable to the cancerous condition of the subjects further investigation is required. Primarily, a checking of individual cases seems mandatory. The previous publication cited (9) represented such an attempt in a limited group of special cases. The chief difference between those data and the present study is an apparent lower titer in estrogenic activity in our pooled urines. We ascribe this difference in part to the difference in method of assay employed for we have found (unpublished data) that with urine extracts, particularly from cancerous persons, the Astwood method gives titers ⅓ to 3 times as high as the spayed rat test. In other words, the immature rat uterus is more sensitive to "enhancing" materials than the spayed rat vagina.

The absolute levels of estrogen output obtained conform roughly to those reported by previous investigators. In women with cancer of the breast, Ross and Dorfman (12) obtained values varying from less than 1.7 to 33.3 μgm. equivalent of estrone per day. Smith and Smith (13) have obtained somewhat higher values at most stages of the menstrual cycle in normal women, as have Dingemanse and Laqueur (5) in an individual woman's cycles. The latter find a ratio of ketonic to nonketonic estrogenic activity of 1:1 during the catamenia and of 1:2 during the intermenstrual period, whereas Smith and Smith find no estrone during bleeding and a ratio of about 1:2 during the intermenstrual period. In our own data the ratios for the noncancerous women's urines are: series I, 1:2.3; series II, 1:5.5; for the cancerous women these ratios are: series I, 1:15.0; and II, 1:8.1. In the men's urines we find the following ratios of activities in the ketonic and nonketonic fractions: noncancerous men, I, 1:4.9; II, 1:3.6; cancerous men, I, 1:6.7; II, 1:6.8. Dingemanse, Laqueur, and Mühlbock (6) report that ⅓ to ½ of the estrogenic activity of pooled normal male urine is in the ketonic fraction. They find an average of 7 μgm. of estrone equivalent per liter of total estrogenic activity. Later Dingemanse and Laqueur (4) report 2 to 27 μgm. equivalent per liter in men with testicular lesions other than chorion-epithelioma.

The age grouping in both our men's and women's series included older persons than those reported by the various investigators cited and probably accounts for the somewhat lower values we obtained.

The definite indications that we obtained of the presence of estriol and estradiol in men's urines is, we believe, notable. Estrone is the only estrogen that has been isolated from the urine of normal men (6). The probable presence of estradiol is indicated by its isolation from testis tissue (2). But the possible origin of estriol is obscure since estriol has not been isolated from male tissue or organs. The concept of estriol as a product of estrone metabolism in the female (11, 13, 14) will require elaboration if estriol is derived from estrone in the male.

Finally, it is evident that a determination of "total" estrogenic activity is far from informative concerning estrogen metabolism. Thus our assays of the total phenolic material in series II give no statistically significant differences between the activity of extracts from the cancerous and noncancerous patients. Yet fractionation discloses several clear differences.

Summary

Pooled urines from 2 sets each of cancerous and noncancerous men and women were separated into three principal phenolic fractions containing presumably estrone, estradiol, and estriol. Bioassay of each fraction was performed, and it was found that (a) the sum of the estrogenic activity of the three fractions was higher in the noncancerous women's urines than in urine from cancerous women; (b) this was reversed in the case of the men's urines because of the higher titers of the nonketonic fractions; (c) the "estriol" fraction of noncancerous women's urines had a higher titer than the same fraction from cancerous women's urines; (d) the "estradiol" fraction of cancerous men's urines had a higher titer than the corresponding fraction of noncancerous men's urines.

A further separation of certain nonketonic fractions indicates that the difference in titers between cancerous and noncancerous men is real and due probably to the estrogens presumably segregated into these fractions.

A useful fractionation of estriol particularly is indicated.

The implications of these findings are discussed.

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Corrections

To the Proceedings of Scientific Sessions of the 34th Annual Meeting of the American Association for Cancer Research, Inc., Vol. 1, No. 9, pp. 729-753, add:

GLYCOGEN AND WALKER TUMOR 256. HOWARD A. BALL. (San Diego, Cal.)

Abstract not available.

To be published in *Cancer Research*.

THE ECTOPIC TESTIS AND TUMORIGENESIS. J. B. HAMILTON. (Yale University School of Medicine, New Haven, Conn.)

The relationship between ectopy of the testis and tumors of the testis was analyzed. Supplementary data regarding ectopy of the testis from experimental work with rodents was presented.

To the discussion of histological technic, p. 747, add:

DR. J. E. EDWARDS (Bethesda, Md.): In reference to Dr. MacCarty's criticisms and remarks about artifacts I wish to point out that all of these tissues were from animals autopsied within 5 to 10 minutes after death. The same sections were shown to Dr. Kenneth Mallory and Dr. Frederic Parker of the Mallory Institute, and they thought they were very good. Furthermore, knowing the excellent work that the Mallory Institute is famous for I was very much pleased to have them ask me if I would supply them with the technic we used.

At the request of the authors, the following correction of an error in the manuscript is published:

Page 804.—Insert Yeast Extract for Spleen Extract in the heading of Table IV in the article: Lewisohn, R., C. Leuchtenberger, R. Leuchtenberger, D. Laszlo, and K. Bloch. Action of Yeast Extract on Transplanted and Spontaneous Malignant Tumors in Mice. Cancer Research, **1**:799-806. 1941.

Abstracts

Reports of Experimental Research

Carcinogenic Compounds

BURDETTE, W. J., and L. C. STRONG. [Yale Univ. Sch. of Med., New Haven, Conn.] COMPARISON OF METHYL SALICYLATE AND BENZENE AS SOLVENTS FOR METHYLCHOLANTHRENE. Cancer Research, 1:939-941. 1941.

In view of reports that the potency of carcinogens may be altered by the agents in which they are carried, methyl salicylate and benzene were compared as solvents for methylcholanthrene.

Four groups of mice were painted twice weekly with methyl salicylate, benzene, methylcholanthrene in methyl salicylate, and methylcholanthrene in benzene respectively. Papillomas, epidermoid carcinomas, spindle cell sarcomas, and tumors composed of two types of neoplastic tissue appeared at the site of application of the carcinogen in both methyl salicylate and benzene. No tumors occurred in mice painted with either solvent alone. No difference was found in tumor incidence, type, and time of appearance in the mice painted with methylcholanthrene in methyl salicylate and methylcholanthrene in benzene.—Authors' summary.

DUNLAP, C. E., and S. WARREN. [Harvard Med. Sch. and Huntington Memorial Hosp., Boston, Mass.] CHEMICAL CONFIGURATION AND CARCINOGENESIS. Cancer Research, 1:953-954. 1941.

Tests of the carcinogenic activity of 70 new compounds related to benzanthracene, dibenzanthracene, methylcholanthrene, and benzpyrene have given further evidence of a high degree of chemical specificity. Slight changes in structure are followed by major changes in activity. Several hydroxy derivatives of active compounds have shown little or no ability to induce tumors.

A new compound containing sulfur, 4,9-dimethyl-5,6-benzthiophanthrene, has proved highly carcinogenic. Radioactive sulfur in this compound could serve as a tracer for studying the local metabolism of an active carcinogen at the site of tumor induction.—Authors' summary.

PALETTA, F. X., E. V. COWDRY, and C. E. LISCHER. [Barnard Free Skin and Cancer Hosp., and Washington Univ. Sch. of Med., St. Louis, Mo.] COMPARISON OF METHYLCHOLANTHRENE HYPERPLASTIC EPIDERMIS WITH BENIGN HYPERPLASTIC EPIDERMIS IN HEALING WOUNDS. Cancer Research, 1:942-952. 1941.

In several experiments involving 124 mice, epidermal hyperplasia, caused by repeated applications of methylcholanthrene, was examined at intervals from 11 to 64 days and regenerative hyperplasia, at the edges of excised areas of skin, was examined at several intervals between 10 and 19 days. Regional diversity in structure was localized, irregular, and seemingly haphazard in methylcholanthrene hyperplasia, whereas in regenerative hyperplasia it was correlated with distance from the excised area. In the methylcholanthrene hyperplasia focal variations were of greater amplitude, the basement membrane and granular layer were slightly more definite, acanthosis and hyperkeratosis were generally more marked, and the spinous cells were somewhat less eosinophilic. Intranuclear viscosity was decreased in both kinds of hyperplasia. This change was progressive to malignancy in the methylcholanthrene hyperplasia and only temporary in regenerative hyperplasia. In both there was demineralization, but this was more irregular in the methylcholanthrene hyperplasia.—Authors' abstract.

TURNER, F. C. [Nat. Cancer Inst., Bethesda, Md.] SARCOMA AT SITES OF SUBCUTANEOUSLY IMPLANTED BAKELITE DISKS IN RATS. J. Nat. Cancer Inst., 2:81-83. 1941.

Bakelite disks were implanted into 13 rats. Of 9 surviving rats 20 months of age or over in this experiment, 4 developed tumors around the bakelite. In a similar series of 10 mice, 6 surviving at 18 months of age showed no tumors. These tumors were fibrosarcomas which were not transplantable. A very low hazard of bakelite carcinogenicity is suggested because of the prolonged exposure necessary for tumor production in rats and their absence in mice. A discussion of the low carcinogenicity of bakelite ingredients is included.—R. C. R.

ZIMMERMAN, H. M., and H. ARNOLD. [Yale Univ. Sch. of Med., New Haven, Conn.] EXPERIMENTAL BRAIN TUMORS PRODUCED WITH METHYLCHOLANTHRENE. Cancer Research, 1:919-938. 1941.

Pellets of purified 20-methylcholanthrene were implanted in the cerebral meninges, the right cerebral hemisphere, and the cerebellum of 103 C3H mice of the male sex.

In all, 48 tumors were produced in this manner: 25 gliomas, 13 sarcomas, 7 mixed gliomas and sarcomas, and 3 unclassified. Among the gliomas were present examples of astrocytoma, glioblastoma multiforme, medulloblastoma, oligodendroglioma, and spongioblastoma polare. Within certain limits the site of pellet implantation was a determinant of the type of intracranial neoplasm which developed.

The rate of growth of the sarcomas was much greater than of the gliomas. The average time when the sarcomas appeared was 195 days as against 279 for the gliomas.

The method of subcutaneous transplantation was employed for the study of the growth behavior of these intracranial neoplasms. From 9 to 14 subtransplants were made of many of these tumors with results that indicated a much more rapid growth of the sarcomas than the gliomas. Frequently, unclassifiable primary gliomas developed characteristic structural patterns in the transplants which made identification possible. This method of study also permitted the separation of so-called "mixed" tumors into their component parts.—Authors' summary.

Hormones

PINCUS, G., and W. H. PEARLMAN. [Clark Univ., Worcester, Mass.] STEROID EXCRETION IN CANCEROUS AND NONCANCEROUS PERSONS. II. URINARY ESTROGENS. Cancer Research, 1:970-974. 1941.

Pooled urines from 2 sets each of cancerous and noncancerous men and women were separated into three prin-

cipal phenolic fractions containing presumably estrone, estradiol, and estriol. Bioassay of each fraction was performed, and it was found that (a) the sum of the estrogenic activity of the three fractions was higher in the noncancerous women's urines than in urine from cancerous women; (b) this was reversed in the case of the men's urines because of the higher titers of the nonketonic fractions; (c) the "estriol" fraction of noncancerous women's urines had a higher titer than the same fraction from cancerous women's urines; (d) the "estradiol" fraction of cancerous men's urines had a higher titer than the corresponding fraction of noncancerous men's urines. A further separation of certain nonketonic fractions indicates that the difference in titers between cancerous and noncancerous men is real and due probably to the estrogens presumably segregated into these fractions. A useful fractionation of estriol particularly is indicated. The implications of these findings are discussed.—Authors' summary.

SHIMKIN, M. B. [Nat. Cancer Inst., Bethesda, Md.] THE LACK OF CARCINOGENIC POTENCY OF DESOXYCORTICOSTERONE IN MICE. J. Nat. Cancer Inst., 2:61-63. 1941.

Subcutaneous injections of desoxycorticosterone acetate failed to accelerate the appearance of mammary carcinoma in strain C3H female mice and no mammary tumors appeared in the males of this same group. Desoxycorticosterone injection also failed to increase the incidence of pulmonary tumors in 20 weeks after a 1 mgm. test dose. No gross or microscopic abnormalities were noted in the adrenals, pituitary, thyroid gland, gonads, liver, or spleen. No subcutaneous sarcomas were observed at the site of injection. It was concluded that desoxycorticosterone is not carcinogenic to mice.—R. C. R.

SHIMKIN, M. B., and H. G. GRADY. [Nat. Cancer Inst., Bethesda, Md.] TOXIC AND CARCINOGENIC EFFECTS OF STILBESTROL IN STRAIN C3H MALE MICE. J. Nat. Cancer Inst., 2:55-60. 1941.

Subcutaneously administered stilbestrol is more toxic to C3H mice than it is when given orally. Retardation in weight increase is directly proportional to the size of the dose and is more marked when stilbestrol is given subcutaneously than when taken orally. This is not due to decreased food consumption but to some toxic action of the compound. If stilbestrol is stopped, the weight increase increment returns to the near normal level.

The animals show loss of weight, atrophy of the viscera, especially the spleen, decreased spermatogenesis of the testes, scrotal herniation, and development of mammary carcinoma. Liver lesions were not observed. In animals killed within a few weeks after cessation of treatment, there was observed squamous metaplasia of the coagulating gland, fibromuscular hyperplasia of the seminal vesicles, and myxomatous degeneration of the ejaculatory ducts. Brown degeneration of the adrenals was noted.

Adenocarcinoma of the breast developed in 18 of 22 C3H mice in an average period of 24 to 27 weeks following administration of 4.27 to 14.25 mgm. of stilbestrol. No lymphatic tumors were seen in any of the experimental animals.—R. C. R.

SHIMKIN, M. B., H. G. GRADY, and H. B. ANDERVONT. [Nat. Cancer Inst., Bethesda, Md.] INDUCTION OF TESTICULAR TUMORS AND OTHER EFFECTS OF STILBESTROL-CHOLESTEROL PELLETS IN STRAIN C MICE. J. Nat. Cancer Inst., 2:65-80. 1941.

Large quantities of stilbestrol transplanted subcutaneously as pellets caused marked lowering in the weight gain increment. This decrease was proportional to the concentration of the stilbestrol in the pellet. Twenty five per cent pellets produce a mortality of 10% in strains C and C3H mice. Fibromuscular hyperplasia of the seminal vesicles, degeneration of the seminiferous epithelium, and partial arrest of spermatogenesis were observed after the first month of exposure to 10% pellets. After 3 to 4 months of similar treatment lack of spermatogenesis was observed and diffuse hyperplasia of interstitial cells of the testes occurred. Eleven months after pellets of various concentrations had been implanted, 13 testicular tumors were found in a total of 52 mice. The incidence of the tumors was roughly in direct proportion to the concentration of the stilbestrol in the tablet.

The tumors were white and pale with a dark brown surrounding tissue. Histologically they showed solid sheets of large polygonal or slightly elongated cells supported by sparse stroma. Large varicosities of capsular blood vessels were observed. Metastasis occurred in the suprarenal region in 3 animals. Seven of the mice developed lymphoid tumors. The appearance of these tumors was probably accelerated by the procedure. Strain C mice are resistant to mammary carcinoma but if these mice were nursed by C3H females and then received stilbestrol pellets the incidence of a mammary cancer occurrence increased to 50%. Foster nursing had no effect on development of testicular tumors.—R. C. R.

Genetics

ANDERVONT, H. B. [Nat. Cancer Inst., Bethesda, Md.] THE INFLUENCE OF HYBRIDIZATION UPON THE NATURAL RESISTANCE OF MICE TO THE PROGRESSIVE GROWTH OF SARCOMA 37. J. Nat. Cancer. Inst., 2:1-6. 1941.

The author summarized work done heretofore on the host-tumor relationship in several strains of inbred mice or hybrids closely related genetically to the test animals. In this group of studies mice of strains L, C57 black, Y, C, I, A, and D were used. Intracutaneous transplantations of sarcoma 37 were made using minced tissue technic. Transplanted tumors in strains Y and D quickly killed their hosts. Tumors in C57 black and L strains grew fast for an initial 12 to 41 days and then completely regressed in most animals. Tumors transplanted into strains C and I grew much slower but in strain C the tumor eventually killed the animal. It regressed in strain I after 12 to 13 days. Strain A mice were shown to be homozygous in relationship to one spontaneous mammary tumor but showed marked variability in their degree of natural resistance to sarcoma 37.

Hybrid mice produced by mating strains I and Y showed 100% susceptibility of the F1 and Y backcross generations and 50% susceptibility of the I backcross generation. This suggests that progressive tumor growth in these mice is controlled by a single dominant factor. If susceptibility is inherited as a single dominant factor as suggested above, then mating two resistant strains should give a high percentage of resistance in the hybrids.

This did no occur when strains L and I were mated. The F1 hybrids were 87% susceptible, F2 were 60% susceptible, and about 80% and 30% susceptibility of L and I backcross respectively occurred.

The conclusion is that the natural resistance of parent strains gives no indication of degree of natural resistance of their hybrids and that one series of hybrids is not sufficient for formulation of any general conclusions regarding inheritance of natural resistance.—R. C. R.

ANDERVONT, H. B., and W. J. McELENEY. [Nat. Cancer Inst., Bethesda, Md.] EFFECT OF INGESTION OF STRAIN C3H MILK IN THE PRODUCTION OF MAMMARY TUMORS IN STRAIN C3H MICE OF DIFFERENT AGES. J. Nat. Cancer Inst. 2:13-16. 1941.

A 25% incidence of tumors occurs in fostered C3H mice which remain with their maternal parent only 17 hours after birth. This suggested to the author the possibility that some of the same strain mice may develop tumors when taken from the parent at birth. Young C3H mice obtained by operative removal from the parental uterus were fostered with C57 black females. None of these animals developed mammary cancer. Only 3 of a group of 15 young C3H mice taken directly from the parent at birth and fostered on C57 black females developed mammary cancer.

In a second series, young C3H mice were foster nursed by C57 black mice for 7 to 14 days and then were nursed on C3H females for 3 days. Tumors of the breast developed in 100% of the group suckling the C3H mothers at 7 days and in 84% of those suckled by C3H females when 14 days old. This suggests an increased resistance to the milk factor as the animals grow older.—R. C. R.

ANDERVONT, H. B., and W. J. McELENEY. [Nat. Cancer Inst., Bethesda, Md.] THE INFLUENCE OF THE PATERNAL PARENT IN DETERMINING THE SUSCEPTIBILITY OF MICE TO SPONTANEOUS MAMMARY TUMORS. J. Nat. Cancer Inst., 2:7-11. 1941.

A review of the literature on this phase of the work conclusively shows that mammary cancer in mice is controlled by the presence of an extrachromosomal influence transmitted in milk, and an inherited susceptibility of the mice to the action of the milk influence. The purpose of this paper is to report observations on the incidence of mammary carcinoma in animals carried beyond the first hybrid generation in an attempt to establish the role of the paternal parent in later generations of mice.

C3H strain females were mated with I strain males. Females from this mating were backcrossed with I strain males. This was repeated with females of the first I backcross generation to give the second backcross generation. Similar backcross breedings were done with Y strain mice using C3H strain females to produce the F1 generation of this series. The F1 hybrids of C3H females and I males were more susceptible to tumor development than the F1 hybrids of the C3H×Y mating. As progressively more backcrosses were done, the Y backcross group became more and more tumor resistant. F2 hybrids from strain C3H crossed with strain I showed a higher cancer susceptibility than the F2 generation of C3H×C57 Black mice.

These relations tend to show that genetic factors are of considerable importance because they determine the susceptibility of the mouse to the nongenetic influences present in milk of the mother. The incidence of tumors in these various groups elucidates the importance of chromosomal factors derived from the paternal parent in mammary carcinoma incidence in mice.—R. C. R.

COLE, R. K., and J. FURTH. [Cornell Univ., Ithaca, N. Y., and Cornell Univ. Med. Coll., New York, N. Y.] EXPERIMENTAL STUDIES ON THE GENETICS OF SPONTANEOUS LEUKEMIA IN MICE. Cancer Research, 1:957-965. 1941.

Two highly inbred strains of mice, Ak and Rf, which differ rather widely (approximately 70 to 2%) in the incidence of spontaneous leukemia (lymphoid and myeloid) have been used to study the inheritance of susceptibility to this disease. The data, covering the parental, reciprocal F1, F2, F3, and various backcross generations, include records on 4,787 mice. The data indicate that susceptibility to spontaneous leukemia is inherited, probably on a multiple-factor basis, and that it is influenced by undetermined environmental factors. The common logarithm of the per cent leukemia in a population is a simple function of the percentage of heredity from the high leukemia stock. No consistent evidence was obtained to demonstrate that either maternal influence or sex linkage were involved in susceptibility. There is some evidence that the female mouse is more susceptible to leukemia than is the male. Susceptibility to monocytic leukemia is also inherited, probably as a multiple-factor dominant character, but with an extremely low degree of penetrance (2.7% in the Rf stock). The type of leukemia as well as the degree of susceptibility is subjected to the laws of heredity.—Authors' abstract.

WOOLLEY, G. W., L. W. LAW, C. C. LITTLE. [Roscoe B. Jackson Memorial Lab., Bar Harbor, Maine] THE OCCURRENCE IN WHOLE BLOOD OF MATERIAL INFLUENCING THE INCIDENCE OF MAMMARY CARCINOMA IN MICE. Cancer Research, 1:955-956. 1941.

In an effort to open up new leads and to further the study of a maternal influence affecting the incidence of mammary gland tumors in mice, an investigation of the blood was started. This is a report of work with the whole blood. Inbred JAX C3H mice which have had their tumor incidence lowered by foster nursing on inbred JAX C57 black mice were injected when 1 to 3 months of age with 0.5 cc. of whole blood secured from normal inbred high tumor JAX C3H male and female mice 2 to 4 months of age. Significant differences now appear between the injected mice and their litter-mate controls. The mice of both groups are well beyond the average tumor age for breeding females of the untreated and unfostered JAX C3H strain.—Authors' abstract.

Radiation

HOLLAENDER, A., J. P. GREENSTEIN, and W. V. JENRETTE. [Nat. Cancer Inst., Bethesda, Md.] EFFECTS OF ULTRAVIOLET RADIATION ON SODIUM THYMONUCLEATE. J. Nat. Cancer Inst., 2:23-27. 1941.

Nucleic acid adsorption bands fall at 2,600 A. It is at this wave length that mutations in unprotected cells are observed. Nucleic acid is most condensed in the chromosomes and it varies during the different stages of mitosis. It was thought by the authors that some idea about the effect of ultraviolet radiation on living cells could be obtained by irradiating sodium thymonucleate *in vitro*.

Changes in the structural viscosity and streaming birefringence were determined in specimens which were irradiated. Irradiation was done by use of three special low pressure mercury-vapor lamps placed symmetrically around the thymonucleate solutions. The solution for test was placed in a fused quartz tube and a control was irradiated in a soft glass tube which absorbed all radiation below 3,300 A. Observations were made on the solutions between 4 and 120 hours of irradiation.

The structural viscosity and streaming birefringence decreased progressively with the progression of the irradiation. This was interpreted as being due to depolymerization of the asymmetrical molecules of the thymonucleate solution into smaller, less asymmetrical molecules. The energy to which the nucleate was exposed was estimated to be 5.3×10^3 quanta. It was considered possible that the energy of the radiation could be transferred easily to the bonds which hold the macromolecule of nucleic acid together. This could break the bond and thus cause the molecular change noted in this experiment. This breakdown of the nucleic acid macromolecule may be responsible for changes in chromosomes which result in mutations.—R. C. R.

Biochemistry and Nutrition—Chemotherapy

GREENSTEIN, J. P., W. V. JENRETTE, and J. WHITE. [Nat. Cancer Inst., Bethesda, Md.] THE RELATIVE ACTIVITY OF XANTHINE DEHYDROGENASE, CATALASE, AND AMYLASE IN NORMAL AND CANCEROUS HEPATIC TISSUES OF THE RAT. J. Nat. Cancer Inst., 2:17-22. 1941.

Liver tissue and tumors arising directly from liver tissue are suitable for respiratory studies because of the large number of active enzymes in the cells. The alterations of these enzymes can be readily followed when the liver cells become malignant. The enzymes amylase, catalase, and xanthine dehydrogenase were selected for this study. The xanthine dehydrogenase of hepatic tumor was found to be half as active as normal rat liver but its activity in normal liver and liver from tumor-bearing animals was the same. Xanthine dehydrogenase in fetal rabbit livers was extremely low. Catalase activity in hepatic tumor tissue was found to be extremely low in comparison to the normal. The effect of transplanted hepatic tumor and of Jensen sarcoma similarly reduced the liver catalase activity. No difference was found in amylase activity between the normal and tumor-bearing livers. Enzymes of rapidly regenerating liver tissue were found to be about as active as in normal liver. The contrast between the enzyme activity of rapidly regenerating liver and malignant liver tissue was sharp and very definite.—R. C. R.

LIPPINCOTT, S. W., and H. P. MORRIS. [Nat. Cancer Inst., Bethesda, Md.] MORPHOLOGICAL CHANGES ASSOCIATED WITH PANTOTHENIC ACID DEFICIENCY IN THE MOUSE. J. Nat. Cancer Inst., 2:39-46. 1941.

Pantothenic acid is necessary for growth in young animals and for life in both young and adult animals. The deficiency produces thinning of the hair about the nose, over the scapula, flanks, and lower abdomen, scaling in the same regions, a feeling of slight thickening of skin about the nose, and occasional crusting about the nose. Apathy, squatting and dragging the hind quarters, and awkward gait are also manifestations of the disease.

Morpologically, the adrenals and osseous systems showed no changes similar to those observed in rats on similar deficiency. The heart and liver showed sudanophilic material on occasional slides. A few renal sections showed enough sudanophilic material to be characteristic of fatty degeneration. The process in the skin appears to be a hyperkeratotic, atrophic, and desquamative dermatosis. The nervous system showed myelin degeneration in sciatic nerves and the spinal cord.

The inability of the animals to survive complete pantothenic acid avitaminosis indicates that this disease is a biochemical one showing morphological evidence in only a few tissues.—R. C. R.

MORRIS, H. P. [Nat. Cancer Inst., Bethesda, Md.] EFFECT OF PANTOTHENIC ACID ON GROWTH OF THE SPONTANEOUS MAMMARY SARCOMA IN FEMALE C3H MICE. J. Nat. Cancer Inst., 2:47-54. 1941.

Tumor growth in mice as measured by calipers was compared in animals receiving a normal diet and those having pantothenic acid deficiency. Rate of tumor growth in control animals was much more rapid than in the mice on pantothenic acid deficiency. One hundred gamma doses of calcium pantothenate caused marked stimulation of tumor growth which approximated that of the control animals. Tumor growth rate in deficient animals became less as the deficiency became more severe. Dietary inadequacy except for pantothenic acid does not appear to be significant in this experiment. Pantothenic acid deficiency is too severe on the host to be considered as a practical adjunct to tumor therapy.—R. C. R.

MORRIS, H. P., and S. W. LIPPINCOTT. [Nat. Cancer Inst., Bethesda, Md.] THE EFFECT OF PANTOTHENIC ACID ON GROWTH AND MAINTENANCE OF LIFE IN MICE OF THE C3H STRAIN. J. Nat. Cancer Inst., 2:29-37. 1941.

Growth curves of C3H mice on an artificial diet deficient in pantothenic acid showed loss of weight. Supplementing the diet with thiamin, pyridoxine, riboflavin, nicotinic acid, and choline increased the growth slightly. With the addition of pantothenic acid the growth curve increased very rapidly. A daily supply of 20 to 30 gamma of the vitamin is adequate for the mouse. Rapid recovery occurs upon adding pantothenic acid supplements. Paralysis of the hind legs, loss of hair, thickening of the skin, and myelin degeneration in the spinal cord are manifestations of deficiency. Death occurred in deficient rats in from 8 to 10 weeks.—R. C. R.

WHITE, J., and G. B. MIDER. [Nat. Cancer Inst., Bethesda, Md.] THE EFFECT OF DIETARY CYSTINE ON THE REACTION OF DILUTE BROWN MICE TO METHYLCHOLANTHRENE (PRELIMINARY REPORT). J. Nat. Cancer Inst., 2:95-98. 1941.

Three groups of mice of subline 212 were used in this experiment. The first group was maintained on Purina dog chow. The second group was fed a synthetic high cystine diet; and the third group was fed a low cystine diet. All mice on alternate days were painted with a 0.2% solution of methylcholanthrene in ethyl ether. Controls ingesting high and low cystine diets were painted with ethyl ether for a period of 100 days.

A high incidence of leukemia occurred in the first group. No aortic sclerosis was observed. The second group showed a 92.3% incidence of leukemia with 2.6% having aortic sclerosis. Mice fed a low cystine diet developed leukemia in only 17.1% of the cases and 94.2% of them showed sclerosis of the aorta.

The latent period for leukemia in the third group was prolonged. The shorter life span of animals fed low cystine diets may account for the low incidence of leukemia in this group. The arteriosclerosis can be accounted for as a toxic action of methylcholanthrene in the absence of cystine as a detoxifying agent.—R. C. R.

Cytology

DuBILIER, B., and S. L. WARREN. [Univ. of Rochester Sch. of Med. and Dentistry, Rochester, N. Y.] THE EFFECT OF COLCHICINE ON THE MITOTIC ACTIVITY OF THE BROWN-PEARCE RABBIT EPITHELIOMA. Cancer Research, 1:966-969. 1941.

Colchicine definitely causes an increase in the mitotic figure (metaphase) count in the Brown-Pearce rabbit epithelioma. The optimal dose is 0.1 mgm. per 100 gm. body weight, and produces the maximum effect in single doses in approximately 6 hours after injection. The effect then gradually wears off. With repetition of the dose at 6-hour intervals, the maximum effect occurs at 12 hours and declines thereafter. The average number of mitotic figures obtained with repetition of 0.1 mgm. per 100 gm. body weight was approximately twice that with 0.5 mgm. This numerical relationship was not obtained with single doses. Although the average response in a group can be predicted for a given dosage, the response of the individual tumor varies greatly so that biopsy must be resorted to in order to determine the magnitude of its response to the drug. The results were so unpredictable that a trial of the effect of colchicine and roentgen radiation did not seem feasible at this time.—Authors' abstract.

Clinical and Pathological Reports

Gastrointestinal Tract

BUIRGE, R. E. [Univ. of Minnesota Sch. of Med., Minneapolis, Minn.] CARCINOMA OF THE LARGE INTESTINE. Arch. Surg., 42:801-818. 1941.

This paper is a statistical analysis of 416 cases which came to necropsy between January, 1910 and July, 1937. The most important early symptom was a change in bowel habit. Seventy-six % of lesions within 10 cm. of the anal ring were not diagnosed by the referring physician. In 172 patients subjected to operation, the two main causes of death were peritonitis (40.7%) and pneumonia (17.4%).—G. De B.

COOPER, W. A. [Nat. Cancer Inst., Bethesda, Md.] THE PROBLEM OF GASTRIC CANCER. J. Nat. Cancer Inst., 2:85-94. 1941.

Two hundred and sixty-four patients with proved gastric cancer were admitted to the New York Hospital from September, 1932, to 1940. Of these, 88(33.3%) were found to be inoperable clinically, and 91 (34.5%) were inoperable by exploratory laparotomy. In 21 cases a palliative gastroenterostomy was done; in 7 cases miscellaneous other procedures were carried out; and in 16 cases a palliative gastric resection was done. Only 41(15.5%) of the entire 264 cases were considered curable by surgical methods. The combined operative mortality for palliative resections was 10.5%. There was a 5-year survival in 44.4% of the operables cases.

The author emphasizes the importance of careful physical examination and evaluation of early symptoms of gastric carcinoma. A discussion of the merits and pitfalls of roentgen examination, gastric analysis, gastroscopy, and stool analysis was presented.

The inoperability of gastric carcinoma is primarily due to a late diagnosis and errors in interpretation and execution of diagnostic procedures.—R. C. R.

HORSLEY, S. J. [St. Elizabeth's Hosp., Richmond, Va.] RESECTION OF THE DUODENUM FOR TUMOR OF THE AMPULLA OF VATER. Ann. Surg., 113:802-809. 1941.

The development of pancreatico-duodenectomy is briefly traced from the original animal experiments of Coffey in 1909 to Whipple's latest modification of his multiple stage operation in humans. Six types of operations are illustrated. A case report is presented in which a one-stage resection of the duodenum and head of the pancreas was performed for an adenoma of the ampulla of Vater. The patient succumbed to uremia on the 5th day.—A. M.

MALLORY, T. B., Editor. [Boston, Mass.] CASE RECORD OF THE MASSACHUSETTS GENERAL HOSPITAL. Case 27171. New England J. Med., 224:742-745. 1941.

This is the case report of a patient who was first seen and successfully treated for typical pernicious anemia with combined system disease and who returned 5 years later in relapse. X-ray and gastroscopic studies showed a polypoid gastric carcinoma. Gastric resection was performed. The high incidence of adenomatous polyps and carcinoma in pernicious anemia is discussed and the necessity for repeated x-ray and gastroscopic studies in these patients is stressed.—A. M.

MALLORY, T. B., Editor. [Boston, Mass.] CASE RECORD OF THE MASSACHUSETTS GENERAL HOSPITAL. Case 27202. New England J. Med., 224:866-868. 1941.

A 50-year-old male had had a gastric resection for a "borderline" polyp, responsible for symptoms of 5 years' duration. Thirteen years after this operation he had a second palliative resection for a carcinoma of the stomach with metastases to regional nodes.—A. M.

MALLORY, T. B., Editor. [Boston, Mass.] CASE RECORD OF THE MASSACHUSETTS GENERAL HOSPITAL. Case 27212. New England J. Med. 224:912-915. 1941.

A case of scirrhous carcinoma of the stomach with multiple peritoneal implants which succumbed to acute intestinal obstruction. Biopsy of characteristic implants at two operations showed only "chronic inflammation." —A. M.

OUGHTERSON, A. W. [Yale Univ. Sch. of Med., New Haven, Conn.] THE DIAGNOSIS OF CARCINOMA OF THE STOMACH AND COLON. Connecticut M. J., 5:506-509. 1941.

This paper is essentially a plea for earlier diagnosis in cases of gastrointestinal malignancy. A survey of metropolitan New Haven revealed that only 2% of patients

with cancer of the stomach and 15% of patients with cancer of the colon were alive at the end of 5 years. But those patients who survived radical resection of the stomach had a 25% chance of living 5 years while those who survived radical resection of the colon had a 60% chance of living 5 years. These 5-year "cures" were obtained in a group of patients in whom the diagnosis was made late. With earlier diagnosis, the percentage of "cures" would likewise increase.

Besides the education of the patient, certain recommendations are made: 1. Any patient with gastrointestinal symptoms of more than 1 month's duration should receive an x-ray examination. Stools should be examined for blood, and gastric analysis, red blood count, and hemoglobin should be done. 2. Any patient with a change in bowel habit of 1 month's duration, with or without anemia or occult blood in the stool, should receive an x-ray examination.—G. De B.

RANKIN, F. W. [Lexington, Ky.] SURGICAL TREATMENT OF ADENOMATOSIS OF THE COLON. South. Surgeon, 10:615-622. 1941.

Because of the frequency of malignant change and other complications such as hemorrhage or obstruction in patients with multiple adenomas of the colon the author advocates total colectomy following a preliminary ileosigmoidostomy. M. J. E.

Miscellaneous

RAEDEMAKER, L. [Peninsula Gen. Hosp., Salisbury, Md.] A CASE OF RETRACTILE MESENTERITIS ASSOCIATED WITH EARLY CARCINOMA OF THE GALL BLADDER. Am. J. Surg., 52:115-119. 1941.

Case report.—H. G. W.

RITCHIE, G. [Univ. of Wisconsin, Madison, Wis.] METASTATIC TUMORS OF THE MYOCARDIUM. A REVIEW OF SIXTEEN CASES. Am. J. Path., 17:483-489. 1941.

From a total of 3,000 autopsies, there were 16 cases in which metastatic tumors were found in the myocardium. The primary tumors varied, with duplication only of 3 carcinomas of the lung and 2 of the pancreas. Ten of the 16 had generalized metastases while in one, a carcinoma of the esophagus, the myocardium was the only site of distant metastasis. The pathway of metastasis to the myocardium was via blood stream or lymphatics or by direct extension; in some cases all three routes were present.—H. B.

SHAPIRO, A. L., and H. BOLKER. [Brooklyn Cancer Inst., New York, N. Y.] TRIPLE PRIMARY MALIGNANCY. Am. J. Cancer, 40:441-446. 1940.

From the literature the authors state that multiple cancers constitute 1.84% of autopsied cases of malignancy of which triple carcinomas comprise 2.9%. Following a brief discussion of multiple malignancy a case is reported of a 70-year-old man in whom were found a lymphosarcoma of the inguinal region, a clear cell adenocarcinoma of the right kidney, and a papillary adenocarcinoma of the pelvic colon. No metastasis from any of the tumors was found although local invasion was evident. A benign polyp of the colon and two lipomas of the forehead were present in the same individual.—L. L. W.

Cancer Control and Public Health

LEHMAN, E. P. [University, Va.] CANCER CONTROL IN VIRGINIA. Virginia M. Monthly, 68:9-15. 1941.

A general outline is given of the work of the Virginia Cancer Foundation in the improvement of educational, diagnostic, and therapeutic facilities.—M. J. E.

SAUNDERS, H. P. [Chicago, Ill.] ORGANIZATION AND FUNCTION OF TUMOR CLINICS IN VOLUNTARY HOSPITALS. Illinois M. J., 79:409-412. 1941.

The author discusses the advantages of utilizing the combined services of a group of specialists for the diagnosis and treatment of the cancer patient.—M. J. E.

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